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January-February, 1926

PROGRESSIVE LIPODYSTROPHY AND HYPERTHYROIDISM

G. MARAÑON AND J. BLANCO SOLER

From the Department of Medical Pathology of the General Hospital
MADRID, SPAIN

The disease, or rather syndrome, which Simons called "Progressive lipodystrophy" is certainly not a new discovery. Zalla (1), for example, quotes the oldest case known described by Morganni. A short time back, when reading the clinical histories of girls given to masturbation, by Zambaco (2), we found the indication, made in passing, that one of them had "a great lack of fat on the upper half of the body, as compared with the lower half." And it is probable that more data, both literary and iconographical, can be found dealing with this question. But the first to make an accurate description of the syndrome was Barraquer (3), of Barcelona, in 1907. His case was that of a girl of 16, whose face began to grow thin in such a fashion from the time she was 12, that she decided to consult our distinguished countryman, who found a very intense fusion of the adipose tissues over the upper part of her body, whilst the lower part contained a normal amount of fat. This author insisted on the complete normality of the skin and of the muscular tissues and suggested a probable intervention of the vegetative nervous system in its pathogeny. His description was thus complete and his case one of the most typical described (Fig. 1).

We draw attention to this to suggest once again that this syndrome should be known as the "Syndrome of Barraquer-Simons," as Simons, although he added interesting anatomic and pathologic data in his reports published in 1911 and 1913 (4), found no need to alter, clinically or pathogenically, the fundamental lines of the first description by Barraquer.

After the publication of Barraquer and before those of Simons appeared cases by Campbell (1907) (5) and Pic and Gardere (1909) (6), and many more at a later date, so that at present we have knowledge of more than 60, which we will not mention especially as it is not our object to make a bibliographical review, which can be found in the monographs of Boissonnais (7), Long and Bickel (8), Weber (9) and Smith (10). In Spain contributions have been made to the causation of this disease by Marañon (11), Pardo (12) and, more recently, Barraquer (13).

In view of several cases which we have seen recently we wish to add data to those already known as to the symptomatology and pathogeny of progressive lipodystrophy.

In the first place, it appears that the name by which this syndrome is usually known is quite improper. Barraquer (3) called it "Atrophy of the cellulo-adipose tissues"; Simons (4) called it "Progressive lipodystrophy," which has been universally accepted. However, both of these names are notably improper, since neither expresses the real characteristic of the process, which is its strange localization. In his latest work, Barraquer (13) calls it "Juvenile adipose dystrophy," which is also much too vague. Probably the most accurate name would be "Cephalo-thoracic lipodystrophia," which indicates the really pathognomonic character of the process, that is to say, its localization in the upper part of the body. However, we do not propose to enter into discussion over the name, still less so in a syndrome whose pathogeny is still imperfectly known.

Since we have devoted special attention to the study of this syndrome, we have been able to observe that it is not a rare disease, but on the contrary is rather frequent although, as usual in all diseases, the extreme cases are seldom met with. But with respect to the distribution of the fat (leaving aside those cases in which this distribution is uniform and normal),

we notice two kinds of imbalance: the first, which is the case of those people whose fat accumulates chiefly in the upper part

Fig. 1. The first case of lipodystrophy described by Barraquer.

of the body, what we might call typical "physiological" fatness, which comes over heavy eaters and drinkers whose volume increases at the neck, chest and upper part of the belly (plethoric

type) and whose legs remain slender; and the other kind in which the fatness affects chiefly the lower part of the body. The latter is so frequent that they form a class apart from normal beings only in their aesthetic aspect. They are nearly always women, frequently young people with no apparent connection with an outward cause. At any rate, in our Southern countries this is so common that there is a popular saying that these women have "the beauty of the thrush, a thin face on a fat body,"* which is a description, even in its translated form, which corresponds to the primitive description of progressive lipodystrophia.

As we have said, when the distribution of the adipose panicle is carefully observed in his patients, one is surprised to see the large proportion which present the cervical-thoracic lipodystrophy, either in an advanced state or in lesser degrees, which are really "frustrated forms" of the syndrome of Barraquer-Simons. It must also be borne in mind that many patients oppose the suggestion that they should be observed naked, and this lessens the extension of our observations.

We would thus suggest *that the syndrome of Barraquer-Simons is probably nothing more than an extremely accentuated form of distribution of the adipose panicle which can be considered as common,* and in consequence there are a whole series of graduations of intermediate forms between the accentuated cases and the normal state.

As is well known, and we have stated above, the syndrome consists of: (1) a tendency of the upper part of the body to grow thin, in which detail we are all in agreement; and (2) a tendency of the lower part to put on fat. Opinions differ as to this second point, for whilst some assert that there is an effective increase of fat, others deny the increase which is only apparent by contrast with the thinness of the upper parts. *Our opinion is that this increase of fat hardly ever exists,* as can be verified when the evolution of the patients is followed for some time. However, occasionally lipomatous formations can be observed, especially in the upper part of the thigh, which increase the volume of the lower limbs.

In our opinion, then, the essential point is the tendency to thinness of the upper parts, and not only the action of becoming

*La hermosura del tordo, con la cara flaca y el cuerpo gordo.

thin but also the inability of recovering the adipose panicle. At the same time the lower part remains normal, unaffected by the cause which makes for thinness, but also untouched by any fattening cause, and yet free to accumulate fat under the action of the inner or outer circumstances which usually make for increase of subcutaneous fat. This is verified if the patient is put on excessive diet and absolute rest; the thinness of the upper parts remains stationary, whilst the lower parts put on fat as in a normal individual. This is shown by the cases of Miraillé and Fortineau (14), Zondek (15) and our own. On the other hand, if the patient is given thyroidine, as we have tried, a normal loss of weight is observed, accentuation of the thinness of the upper parts, and certainly a thinning of the lower limbs, although perhaps less marked than in normal subjects, especially when affected by adipose tumours.

The fusion of fat in the upper part of the body may reach the absolute limits described by some authors. This total reabsorption is characteristic and justifies the qualificative "progressive" given by Simons to this disease. But the extreme limit of this disease appears only in a very limited number of cases and not in all the intermediate cases which, as we have stated, are very numerous. When the fat has disappeared totally the disappearance of the "fat ball" of Bickat is typical, as also the disappearance of the other adipose process of the face, which generally resist persistently all other causes of thinness, even those which are very severe, such as exhausting illnesses, protracted hunger, etc. This circumstance gives the face of the patient that "skull-like aspect" of the total marking of the cheek bones and the whole of the skeleton of the face, under the skin. The coincidence of this total absorption of the fat of the face with a generally normal state of health is in itself sufficient for the diagnosis of the disease.

Apart from these details of the lipodystrophic process there do not appear to be other subjective or objective symptoms of the disease. All other manifestations described by other authors and which we have noted in our own cases, seem to us to be dependent on the other pathological states which almost without exception accompany the lipodystrophy, and which are in a certain sense the "activators" which reveal the disease, but in

no way whatever do we consider that they are directly related to the lipodystrophy itself.

The first observations of this disease were attributed by Barraquer and Simons (3), (4), (13), although with the natural reserve, to neuro-vegetative disturbances. Long and Bickel (8) recently insist on the same hypothesis, in support of which, apart from data as to pathogeny which they themselves admit are doubtful, they allege the frequency with which these patients present nervous vegetative symptoms (which we must admit are almost always of rather vague significance).

Another group of authors have tried to explain the syndrome under consideration by disturbances of the glands of internal secretion. However, in the first place a constant endocrine symptomatology has not been found in cases of lipodystrophy, nor glandular lesions which are not exceptional (it should be borne in mind that autopsies have been very rare), nor the slightest experimental data which support this supposition. In the second place, there is a fact which contradicts the exclusively humoural explanation, and this is precisely the localization of the lesion in only one segment of the body, which could only be explained by intervention of the nervous system. The only anatomo-pathological data at present available on this syndrome are those of Zalla (1), who found a tumour of the hypophysis in a corpse, which had not been under observation during life, but the aspect of which guaranteed the accurateness of the diagnosis, and the case of Sarbo (16), who found a lesion of the corpus striatum.

It seems more logical to admit the collaboration of both these factors, the neuro-vegetative and the endocrine, which it is known appear so frequently united in the clinic, especially in the group of diseases which Pende (17) called "sympathetic-endocrine diseases," or which we might call still more accurately "vegetative-endocrine," such as the different localized lipomatosis, symmetrical lipomatosis and tropho-œdema. This united action would explain why the humoural factor should act only on a certain segment of the organism; at any rate there have been several observations in the clinic which show that this can happen especially in lesions of the hypophysis. For example, Pansini (quoted by Pende, 17), describes a case of hemilateral acromegaly, Biedl (18) mentions another case, and we have also

observed the same (19). Neiden (quoted by Beck, 20), refers to an observation of obesity of hypophyseal origin limited to one side only, and Beck adds that this would not be an exceptional observation if both sides of the organism were measured carefully. Bartolotti (21) published the very interesting case of a man whose left side was attacked by obesity as a consequence of atrophy of the left testicle; and Athias (22) quotes a case of Weber in which a bird had male feathers on the right side of the body and female feathers on the left side, and in which, at autopsy, a testicle was found on the right side and an ovary on the left. The cases of hypophyseal lesion might be interpreted as suggested by Long and Bickel (8) on the supposition that they are not due to an endocrine disturbance but to the lesion of the para-hypophyseal metabolic centers. However, without going into a discussion as to the exaggeration of this effacement of the hypophysis decreed by the physiologists, the cases of Bartolotti and Weber are sufficient for us to affirm that humoural disturbance can act on the tissues in a segmental manner, naturally in collaboration with the nervous system, although the mechanism of this collaboration is not yet known to us.

We do not wish to insist on this suggestion, which for the moment is absolutely theoretical. But we do wish to produce certain data which indicate that *the cephalo-thoracic lipodystrophy is frequently combined with hyperthyroid states and more frequently than with any other pathological state.*

Several years ago Babinski (23) published a case of "Basedow's disease with myxœdema in the lower limbs" which we now suspect was hyperthyroidism with lipodystrophy. Gertsmann (24) has described a typical case of lipodystrophy combined with hyperthyroidism. The case of Smith (10) was also hyperthyroidism with hypermetabolism (+ 36%). Christiansen (25) and Feer (26) have also observed the coincidence of lipodystrophy with thyroid ailments, although the latter were not of hyperfunctional type. But we wish to base our arguments chiefly on our own experience.

The first case we reported in 1920 (11), was that of a hyperthyroid patient, although the syndrome of Basedow was not pure but accompanied by melanoderma, virilism and ovarian in-

sufficiency. The observations which we have taken at a later date follow.

CASE I

Woman of 48 years. There are several family antecedents pointing to hereditary syphilis (father and two brothers died of juvenile hemiplegia), although she, herself, has had no suspicious manifestation and the Wassermann test was negative. She was very nervous from early girlhood; her first menstruation was at 12 years; she married young and has had 8 children, 7 of whom were still-births. She was stout until 40 years old and began to get thin at 42, becoming more nervous. At 47—that is to say, in the previous year—menstruation stopped and the loss of weight became accentuated until

Fig. 2. Patient, Case I, 12 years previously, in normal health.

at the time of observation she weighs only 45 kilograms for a stature of 1.68 meters (Figs. 2, 3 and 4). The symptomatology we have noted can be divided into the following groups:

On the one hand, we find a typical *hyperthyroid syndrome* corresponding to the form which we have described as "menopause hyperthyroidism" (27): great thinness, discreet thyroid, hypertrophy, tachycardia, trembling, slight exophthalmia, great motor restlessness, sleeplessness, strong hypertensive and emotive reaction with the injection of half a milligram of adrenaline, oculo-cardiac reflex distinctly positive (108-120) and a very high basal metabolism (+ 95%).

On the other hand, an aortic insufficiency can be diagnosed in this patient, well verified by auscultation and percussion, tolerated well by the patient and undoubtedly related to the syphilitic antecedents.

The state of precocious senilism is also very evident in the patient, whose wrinkled face, hard arteries, scanty white hair and general tired face seem to belong to a woman of 60. (Figs. 4 and 5.)

Fig. 3. Patient, Case I, 8 years previously, at the beginning of weight loss.

Fig. 4. Patient, Case I, at the present time.

Finally, even when the patient is dressed one notices clearly the contrast between the extreme thinness of the face, arms and upper part of the body and the normal corpulence of the lower part of the body and the legs. When undressed this contrast is even more marked, the body appearing as if divided by a horizontal line at the height of the waist above which the subcutaneous fat has almost completely disappeared, but has remained below the line in sufficient abundance to form the large suprapubic prominence and the adiposity of the

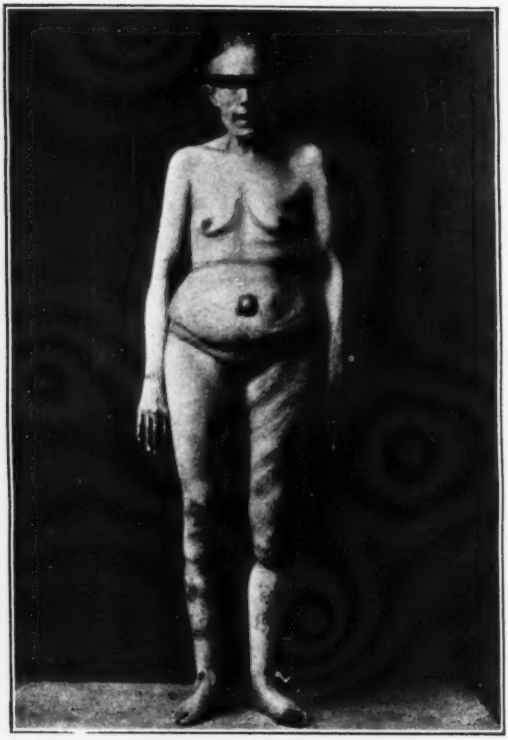

Fig. 5. Patient, Case I. General aspect.

thighs which are noticeable in the illustration. In brief, it is a typical example of cephalo-thoracic lipodystrophy (Fig. 5).

Diagnosis: Climateric hyperthyroidism; precocious senilism; Syndrome of Barraquer-Simons; aortic insufficiency.

CASE II

C. V., 38 years old, married. Her mother died suddenly, and had suffered very much from "palpitations." The patient had menstruated at 15, married at 21, and had 7 children without complica-

tions. She gave a negative Wassermann test. Two years previously she had begun to lose weight and to experience various disturbances, having lost as much as 23 Kgs. up to the time of observation. Our examination gave the following results: Presentation of a hyperthyroid syndrome with large retro-external goiter; fixed stare; slight exophthalmia; trembling; tachycardia; palpitations; sensations of heat; great emotivity; slight lymphocytosis; etc.

On the other hand, we find evident symptoms of mitral insufficiency with blowing systolic murmur and typical radiographic shadow.

Finally, even when the patient is dressed it is obvious that, in spite of the intense loss of flesh, this has not been at the expense of the lower part of the body, which has kept its fat, whilst the upper part shows extreme emaciation. The patient herself expressed her surprise at the phenomenon which was so evident on examining her naked.

Diagnosis: Retrosternal goiter with hyperthyroidism; Syndrome of Barraquer-Simons; mitral insufficiency.

CASE III

A. S., 30 years old, married. Has had two abortions and one child. At an early age had several infectious diseases and appendicitis. Her mother died insane. She gave a negative Wassermann test. Six years previously, when apparently in good health, she began to lose weight, which in the last four years has reached a loss of 11 kilograms.

With the exception of continued attacks of pharyngitis the patient has nothing more than a hyperthyroid syndrome which, whilst clinically is not very intense, is still perfectly distinct; diffusive hypertrophy of the thyroid, fixed and glassy stare, normal but very unstable pulse, and typical trembling of the hands. The circulatory and nervous reactions to adrenaline are negative. However, the diagnosis of hyperthyroidism is completely confirmed by the determination of the basal metabolism which gives +40%. The oculo-cardiac reflex gives 60-68. The reflex of Hering is positive. The urine is normal.

Examination of the patient when dressed shows the contrast between the extreme thinness of the face (skull-face), thorax above the waist and the width of hips and thickness of the legs (Fig. 6). Undressed examination confirms the existence of the lipodystropic syndrome, typical but not intense. The patient refuses to be photographed undressed.

Diagnosis: Hyperthyroidism; Syndrome of Barraquer-Simons.

CASE IV

C. B., 27 years old, has always been healthy and her menstruation regular. She was stout and in normal health when she began to take large amounts of iodine two years previously on the advice of a friend, which gave origin to a typical *syndrome of "Jod-Basedow,"* great loss of weight (12 kgs.), nervousness, anxiousness, sensation of heat, trembling and tachycardia. We should state that she comes from a region where thyroid tumours are endemic (Asturias) and that she had always had a rather heavy neck, and her mother also has a voluminous simple goiter, all of which explains her sensitiveness to iodine. At present she is much better. (After discontinuing the iodine for several months her basal metabolism is normal.)

She is herself surprised that the loss of flesh is confined exclusively to the upper part of the body. In effect, her face, thorax and arms are skeleton-like, the disappearance of the fat of the face being extraordinarily intense. On the other hand the adipose panicle

is well maintained from the hips down, giving the typical contrast of the *progressive lipodystrophy.*

Diagnosis: Iodine hyperthyroidism and Syndrome of Barraquer-Simons.

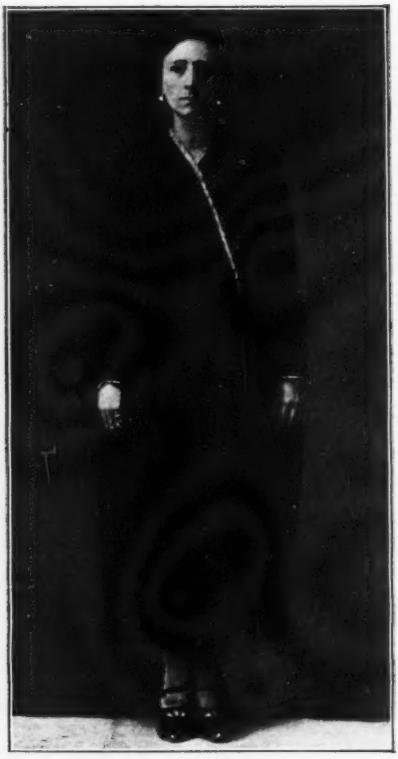

Fig. 6. Patient, Case III. Cephalo-thoracic type of loss of flesh.

CASE V

C. N. de G., 57 years old, is married and has no children. She has always been healthy. Her menopause occurred at 48 and about that time a tumour began on the right side with typical hyperthyroid symptoms: thinness, trembling, tachycardia, emotivity, etc., with basal metabolism +20. (At present she is much better.) She showed arrhythmia, dyspnœa of effort and slight cyanosis; initial myocarditis; arterial tension, 180-90.

The patient herself calls attention to the fact that her loss of weight (total 15 kgs.) has been almost all at the expense of the upper part of the body. The fat of the face is completely effaced, giving it

that skull appearance which is characteristic of the lipodystrophy. The lower part of the body maintains its fat perfectly. There is slight œdema in the ankles.

Diagnosis: Goiter and climacteric hyperthyroidism; Syndrome of Barraquer-Simons; myocarditis.

CASE VII

C. R., 18 years old. Her mother had a large goiter. She herself has suffered during the past two years from a discreet hypertrophy of the thyroid accompanied by tachycardia (110 pulsations), palpitations, trembling and great nervous excitement. During the past year she has begun to lose flesh "from the face and arms only," as she herself remarks.

In effect, the examination of the patient confirms the almost absolute disappearance of the fat from the face, thorax and arms, the inferior part of the body being almost normal (or rather slightly excessive).

She showed basal metabolism, 30; slight lymphocytosis; normal urine.

Diagnosis: Juvenile hyperthyroidism; Syndrome of Barraquer-Simons.

Besides these cases, we have seen two more, one published by Pardo (12), and another the history of which we do not copy here, as it reproduces that of any of the known observations in which there were no hyperthyroid symptoms. In consequence, the proportion in favor of the coincidence of lipodystrophy and hyperthyroidism is obvious: 8 cases against 2 of the 10 we have observed.

Loewy and Zondek (28) had already called attention to the frequency with which certain hyperthyroid patients present adiposity in the lower part of the body, but they insist in differentiating these cases from progressive lipodystrophy, arguing that it is simply the appearance of lipomas on the lower limbs, especially at the hips, which give the body the aspect of a false syndrome of Barraquer-Simons. We consider that this interpretation is not correct and that their cases are perfectly similar to ours of lipodystrophy with hyperthyroidism. Examination of the photographs of the cases of Loewy and Zondek convinces us that we are right, although their cases are probably not advanced and the absorption of the fat of the upper parts has not yet reached its maximum intensity. However, there is evidently in these cases a dissociation between the resistance of the lower part of the body and the upper part with respect to the reducing action of the hyperthyroidism. *The fact that the fat takes the form of lipomas and not of diffusive subcutaneous infiltration does not appear to us to be a differential criterion, because the*

lipomatous formations, either large or small, are present in all forms of obesity, and in many cases it is impossible to determine where the infiltration ends and the lipoma begins. We do not know exactly the reasons for the formation of lipomas, which are probably of a nervous order and frequently provoked by a peripheral irritation, but as we have stated, this formation takes place in the great majority of stout persons. There is no need to recall the marked frequency with which stout women, especially at the change of life, when they reach a certain degree of adiposity, commence to present lipomas; the classical division of the painful adiposity of Dercum is in simple adipose forms, lipomatotic forms and mixed forms, and finally in our clearest cases of lipodystrophy we have already indicated the presence of more or less developed lipomas. Observation I, as can be seen from the photographs, is a typical example of how the maximum grades of lipodystrophy and hyperthyroidism can be combined.

Whilst calling attention to this frequency of the combination of hyperthyroidism and lipodystrophy, we repeat that we do not wish to insinuate that the thyroid alteration may be the cause of the trophic disturbance. As we have already indicated, it is probably a neuro-vegetative constitution which predisposes the subjects to this cephalo-thoracic type of thinness, and the hyperthyroidism merely acts as an "activator," exaggerating the tendency of the upper part of the body to lose flesh and the relative resistance of the lower part to this loss, and this resistance is, of course, more apparent when the fat takes the lipomatotic form.

It could be objected that if this hypothesis were true, any other cause of emaciation would have this same "activating" effect, but it should be borne in mind that hyperthyroidism is precisely a disease which coincides with very constant and profound neuro-vegetative perturbations, which may have part in the lipodystrophic predisposition. In consequence, from this point of view, there is no comparison between a hyperthyroid cachexia and a cancer cachexia, for example. Just as in hyperthyroidism, on the other hand, there would be other cachexic states of endocrine nature, frequently united to neuro-vegetative perturbations also, such as those due to hypophyseal lesions which have also been shown to cause lipodystrophy.

SUMMARY

Progressive lipodystrophy, cephalo-thoracic lipodystrophy, or syndrome of Barraquer-Simons (syndrome rather than a disease), appears to be a predisposition to a peculiar way of losing flesh, determined by neuro-vegetative factors whose nature we do not yet know.

There are cases, chiefly in women, in which this alteration is what we might call a physiological or attenuated form.

If in such predisposed cases there is an additional cause for losing weight, such cause will act as an "activator" which will accentuate the typical form of loss of flesh. Amongst these causes, the most frequent is hyperthyroidism, undoubtedly because it coincides with favorable neuro-vegetative perturbations which determine the lipodystrophic predisposition.

Whether this hypothesis is correct or not, it is a fact that in practice cephalo-thoracic lipodystrophy frequently coincides with hyperthyroidism, and in every case of lipodystrophy the minor hyperthyroid symptoms should be sought and the basal metabolism be determined. At the same time in every case of of flesh. In the lower parts the fat is normal, or at least offers a greater resistance to the loss, especially if lipomatotic formations are produced, as is frequently the case.

From the symptomatological point of view, we consider the essential element of lipodystrophy to be the cephalo-thoracic loss hyperthyroidism the manner of distribution of the fat should be examined. Proceeding in this fashion, we feel sure that our impression will be confirmed as to the frequent co-existence of both states.

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GIGANTISM*

N. A. SCHERESCHEWSKY

Privat-Dozent at Second Moscow University

Gigantism is the most interesting and most complex syndrome in pluriglandular affections. It is as interesting as it is little understood, in spite of the careful and lengthy study devoted to this subject by eminent authorities. We find gigantism in all periods of history and among all nations, especially is the Russian epical literature rich with examples of gigantism.

Giants were considered "supermen"; they were clothed with special qualities, with enormous physical strength; the best national characteristics were incorporated in them; every act of theirs became magnified in the songs of the common people.

But our conceptions change with time. At present there is the growing tendency to consider these giants mere pathological types, a form of special affection, that requires a thorough study.

Such patients were not only subjects for extreme curiosity, but also served to be exploited on account of their enormous physical strength. So did Frederick the Great, unmercifully recruit such patients into his army. It was one Piercourt de Saint-Quen, a French baron, that conceived the idea of creating a special fund of several millions of francs to be devoted exclusively to the artificial propagation of giants. This eugenic idea of the baron, however, was a total failure, partly because of the prevalent sterility among giants, and partly because their children as a rule were normal.

The tallest giant on record was Kayanus, a Finn. His height reached 283 cm. It is remarkable that we encounter very few female giants; there are only two females in the following list who have been studied.

1. Fr. Winkelmeyer, Northern Austria, age 20, studied by Virchow, height 278 cm.

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2. Hans Krav, Zimbrass Castle, studied by Kiari, height 275 cm.
3. Konstantin, Württemberg, age 26, studied by Dufreny, height 259 cm.
4. One Scott, skeleton, of Dublin, studied by Freulich, height 259 cm.
5. One Austrian, studied by Topiner, height 255 cm.
6. Marianna Wede, Brenkendorf near Halle, age 16½, studied by Ranke, height 255 cm.
7. Loushkin, a Kalmiuck skeleton, age 33, Orfill's Museum at Paris, studied by Lemolt, height 254 cm.
8. Charles Birn, skeleton, studied by Cunningham, height 253 cm.
9. A Swede, an army guard of Frederick II, skeleton, studied by Topinar, height 252 cm.
10. Cooper, Yorkshire, studied by Ginstel, height 250 cm.
11. "Kaleb," studied by Uds. Gettingson, height 250 cm.
12. Chenoch, Salzburg, studied by Maas, height 250 cm.
13. Wilkins, St. Paul, Minnesota, studied by Virchow, height 245 cm.
14. Hassan Ali, Egyptian, Derr, near Wadi Chalpha, studied by Maas, age 17, height 240 cm.
15. Abul-Choul of Assuan, studied by Sirena, age 20, height 240 cm.
16. Machnoff, Vitebsk, studied by Gushan, age 22, height 238 cm.
17. Drezel, Ohniun, studied by Ranke, age 37, height 238 cm.
18. Schwan-Insing of China, studied by Taruffi, age 33, height 230 cm.
19. Thomas Gessler, Ginund, studied by Boule, age 25, height 235 cm.
20. Amenates, Kerezund, studied by Ornstein, age 18, height 233 cm.
21. Hugo, St. Martin de Versuv, France, studied by Lonoi and Roi, age 25, height 230 cm.
22. Vasilica Calliandja, Corinth, age 22, height 230 cm.
23. Yochin Cleicheagvy, Spain, studied by Garnig, height 230 cm.
24. Albert Brug, Scotland, studied by Saltarino, height 230 cm.

Giants are always descendants of normal sized parents.

Their birth, according to the established view in literature, is not accompanied by any abnormalities. Their growth hardly differs from that of other infants. Their childhood is, as a rule, perfectly normal. Only later, usually before or during adolescence, a tendency of intensive growth develops. This increased growth may be steady or may occur periodically, leaving an interval of comparative rest in growth.

The following case presents so many unusual features that it deserves a full description.

PRESENTATION OF CASE

Patient, V. G., 22, farmer, came into the Therapeutic Clinic of the Second Moscow University at the beginning of February, 1925, with complaints of slight dyspnoea, cough and weakness. He had been sick for the last four years. He is single, has smoked since the age of 17, and occasionally drinks.

Heredity. The grandparents on both sides, paternal as well as maternal, were strong people. His father's mother is still living, her age 80. The patient's father died of tuberculosis of the larynx at the age of 48; he was a drunkard. The mother is living and healthy. She had seven children and two spontaneous miscarriages. She has five living children, of whom one is a daughter of 9 years, of slight build. There was never a case of excessive growth in the family, neither were there any tall ones among all the relatives, according to the statement of the patient's mother.

Anamnesis. The patient, the second child, was delivered at full term. He was breast fed and grew extraordinarily rapidly, and his rapid growth, especially at the seventh and eighth months of age, was the talk among the neighbors. In the accompanying photograph (Fig. 1) is seen the patient at the age of eight months sitting on the lap of his mother, while his elder brother of two years is sitting on the father's knee. The man standing is the patient's grandfather on the mother's side. It is clear that the patient at the age of eight months was already physically superior to his two-year-old brother.

This extraordinary growth continued so that at the age of three to four years he was so much taller than his elder brother that no one would believe him to be the younger. At eleven to twelve years his physical strength and growth were the subject of general admiration of the neighbors. At twelve he almost drowned, contracting pneumonia, from which, however, he soon recovered. In spite of this sickness his strength and growth continued to increase. When he was twelve to thirteen years old his father died and he immediately assumed the management of the farm, taking over all the work. This task, according to the patient's own statement, did not seem to him excessively hard. When sixteen to seventeen years old his physical strength was especially in evidence. To carry a bag of flour weigh-

ing five poods (200 pounds) on his shoulder for a distance of four to five versts (miles) was easy for him. His height at this age increased considerably. There was no one to equal him in the whole county, either in strength or in growth.

In 1921, when the patient reached his eighteenth year, he again contracted pneumonia, followed shortly after by an attack of typhoid fever. Soon after recovery from these diseases he accidentally fell off a swing from a height of fourteen feet and was unconscious for two hours, but fully recovered and for a time felt himself the same

Figure 1. Patient at the age of eight months.

as ever. Soon, however, he gradually began to notice an oncoming weakness and the ceasing of growth. At the same time he noticed a slight thoracic kyphosis.

Present Status. The patient's height is 193.4 cm., and his weight, 87.5 kg. His powerful build is evident in his whole appearance. His head is not large, its circumference being 56.8 cm. The superciliary arches are definitely thickened and are quite prominent. The bones of the skull as well as all the bones of the face are quite thickened.

The eyes are widely separated. The root of the nose is somewhat depressed. The nostrils are widely open. The lower jaw is directed decidedly forward and is of powerful size. The teeth are considerably spaced, especially in the lower jaw. The tongue and the ears are very small, out of proportion to the other parts of the head. He has a good growth of hair on his head. There is no beard, however, nor a mustache, and he never has had either. On swallowing there appears on the neck a circular swelling coming out from behind the manubrium sterni. This is the right lobe of the thyroid gland, which

Figure 2. Patient W. G-ow is 22 years old, and his mother is 50.

is quite enlarged and situated low. The larynx is large, the thyroid cartilage measures much more than usual. The circumference of the neck is 43 cm.

The thorax is strikingly large, the ribs are thickened, the intercostal spaces widened; the diverging angle of the ribs is considerably more than a straight angle. The respiration is of mixed type. On the back one immediately notices the enormous scapulae and the spinal column, which is in its upper thoracic segments disfigured by kyphosis. Hair under the axillae is moderately present. There is com-

plete absence of hair on the chest. The abdomen is not enlarged and is not fat. The suprapubic growth of hair is of the feminine type. The penis is large, the testicles are each the size of a large plum. Erections and libido are present. The pelvis is of the male type and powerful. The extremities are proportionately large and wide. The hands are very large.

The patient's skin is devoid of any abnormalities, as eruptions or scars. Pirquet's reaction is negative. The roentgenological examination of the skeleton reveals a considerable thickening of all the bones, equally distributed.

The roentgenography of the skull reveals a definite enlargement and thickening of the lower maxilla, of the malar bone, and of the superciliary arches. The sella turcica, due to rhythmical pulsatory movements of the head, could not be obtained clearly. It appears, however, somewhat wider and deeper than normal. The anthropometric measurements of the patient in millimeters are as follows:

	Weissenberg's Patient		Our Patient	
	Abs.	Rel.	Abs.	Rel.
Height, standing	1658	1000	1934	1000
Height, sitting	873	526	1919	529
Measurement of lower segment	785	475	924	479
Circumference of thorax	836	508	1115	575
Length of arms	748	451	860	446
Length of legs	863	520	950	492
Width of shoulders	361	218	450	233
Width of hips	276	166	340	176
Circumference of head	551	332	586	304
Length of hand	185	112	220	114
Length of foot	258	157	300	156
Weight	58.51 kg.		87.5 kg.	

The Respiratory Organs. The thorax is bulky. Over the right apex there is a slight depression. Percussion here reveals a slight dullness. The lung borders are within normal limits. The lungs are very large (manifestations of splanchomegaly). Auscultation everywhere reveals vesicular respiration and dry scattered râles. Over the right apex is heard bronchial respiration. The sputum is negative.

Circulation Organs. The lines of demarcation of the heart (by percussion) are within normal limits, the left border being one finger width inside of the left nipple line, the right border in the third intercostal space, but of course the whole dullness of the heart is proportionately large. The large vessels by roentgenography do not show any abnormality. On auscultation dull sounds and light systolic murmurs are heard at the apex and especially over the "pulmonary area." The pulse is 80, regular, full and tense.

Digestive Organs. He has excellent appetite and no dyspeptic symptoms. The stomach juices proved upon examination to be en-

tirely normal. The examination of the duodenal contents, obtained through the introduction of a thin catheter, gave the following results:

Trypsin, 2560
Diastase, 640
Lipase, 7.4

A few leucocytes were found in the sediment. The examination of the feces showed the presence of ascaris eggs. The liver and the spleen are not palpable. The abdomen is negative.

Genito-Urinary Organs. The urine is normal. Urination does not show any deviation from normal. The penis, as mentioned before, is proportionately large; testicles, the size of large plums. The patient states that he has libido and quite frequent erections. He has frequently thought of marriage, but poverty has stood in the way. He denies onanism.

Figure 3. On the left is the patient's hand, on the right is the hand of a normal healthy man of the same age as the patient.

Blood Examination.

Wassermann's negative.

Hemaglobin,	80%
Erythrocytes,	4,600,000
Leucocytes,	7,300
Neutrophiles,	61.5%
Small lymphocytes,	22.5%
Large lymphocytes,	6. %
Eosinophiles,	8. %
Transitional cells,	1.5%
Basophiles,	0.5%

The large percentage of eosinophiles, which is quite common in acromegaly, may be noted. But this symptom becomes of no value in our case, because of the presence in the feces of ascarid eggs. There is nothing unusual in his nervous system, except the lower knee reflex. Psychologically the patient presents many abnormalities. The consciousness and the orientation as to space, time and surroundings are clear. The patient is and has been mentally backward since childhood. The disease did not add any other changes in his psychical condition. His self-consciousness and his mood are firm; he is even, quiet, not irritable and not excitable. He lacks a clear idea of his present condition, considering himself practically well. His asthma troubles him only on walking; he has no other complaints. He believes that if he were at home he would be quite well. The circle of his interests is very narrow; he leads a hand-to-mouth existence. He desires to learn carpentry, but in case he does not succeed, he would be as well satisfied with his present peasantry. He loves quietude, order and rest. He always avoids disputes, quarrels and fights, in spite of his superior physical strength. Being always able to prove his right by his might, he nevertheless never takes advantage of it. He enjoys the love of his neighbors for his even temper and helpfulness.

He graduated from a primary peasant school; he was far from good in his studies, which he pursued against his wish and without any order. He never had any love for books. He is not able to name a single Russian writer, neither can he name any country or government, except the Soviet Republic and its President, Kalinin. He counts correctly with relative ease and dexterity. Within the limits of his possibilities his thinking is quite logical. He has no delirious or fixed ideas, neither has he any hallucinations. His personality is intact. He is drowsy, apathetic, somewhat dragged.

Sensory Organs. The sight and eye backgrounds are normal. There is no bitemporal hemianopsia. Hearing and smell are normal.

Considering all the facts obtained from the patient. we see that they amount to a chronic myocarditis, bronchitis and the consolidation of the right apex in a subject of twenty-two years, of gigantic stature, with prominent acromegalic stigmata—enlarged superciliary arches, molar bones, nose, lower jaw, larynx, wrists and ankles. There is present also a small right sided goitre.

The whole history of his growth is uncommon. In the literature, as a rule, we find the appearance of gigantism corresponding with the advent of sexual maturity; here the infant of eight months outgrew his brother of two years. His growth progressed slowly and without regard to his sexual development. With this growth his physical strength increased proportionately.

The study of gigantism began with the appearance of the work of Langer (1872), who differentiated two kinds of giants, the "normal" and the "pathological" (acromegalic). The ex-

istence of so-called "normal" giants is questionable. Though Langer described three skeletons of "normal," "harmonious" giants, yet we know that in all giants sooner or later there appear acromegalic symptoms. Sternberg had shown that in 40 per cent of giants is present acromegaly, and that 20 per cent of acromegalic patients are giants. Thus gigantism and acromegaly are so closely interwoven that it is impossible to determine the end of one and the beginning of the other. Launnois and Roy state that the majority of the giants they observed had acromegaly. The period of their stormy growth coincided with their sexual maturity. Their sexual vigor died out early; as a rule they were childless. They became weak at an early age and died of accidental causes, resembling the early withering of an artificially raised flower. The giant observed by Huchard and Launnois began his stormy growth at the age of 12. At 18 his height was 197 cm. He had two children. He reached the age of 60, when the symptoms of acromegaly appeared.

Brissaud and Meige expressed the view that acromegaly and gigantism are symptoms of the same affection, a disorder of the hypophysis. In young individuals this affection brings forth gigantism, while in older individuals where the ossification of the epiphyseal sutures is complete the same affection will result in acromegaly.

The assertion of these authors that gigantism is an acromegaly of growth is positively wrong, because we know from literature of many cases of acromegaly in children, and in 1912 Salle described a case of an innate acromegaly of a newborn. Post-mortem examination revealed a dilated sella turcica; the hypophysis contained a number of shoots of eosinophilic elements that were diffused in the whole anterior portion. Bertoletti in 1910 described a young man of 19 who, at 14, developed typical acromegaly. His height was 166 cm. All the epiphyseal junctures were open. There was no gigantism. Fisher reported a case of acromegaly in an 11 year old boy. His height was normal. Claude described a 19 year old girl, where acromegaly appeared at the age of 15. Here again there was no gigantism. The epiphyseal junctures were closed. Thus we see that acromegaly may appear at an early age and that

its development does not depend upon the condition of the epiphyseal junctures.

The close relationship, however, between gigantism and acromegaly may be considered definitely established. The more carefully the giants have been studied, the oftener have been found in them the changes of the sella turcica and the oftener they have been classified as acromegalic.

Levy and Franchini pointed out the fact that giants frequently develop hypophyseal obesity, which is often met also in acromegalics.

Assuming that in both cases the posterior portion of the hypophysis becomes compressed by the changed anterior glandular portion, we can see in it another proof of the pathogenic relationship of these diseases. There is an undoubted presence of some common pathogenesis, but it is hard to determine the nature of it. It is merely clear that in both cases there are certain hyperplastic changes in the anterior portion of the hypophysis. Why in one case develops gigantism, in the other acromegaly, we do not know. It is possible that in gigantism there is a pure hyperplasia of the cellular elements which causes a hypersecretion of the anterior portion of the hypophysis, resulting in the hypersecretion of the normal hormone that leads to gigantism. This is confirmed by a series of experiments in which, after feeding animals on an abundant diet, consisting of hypophysis preparations (the whole pituitary, or the anterior portion of it, but not the posterior), the manifestations of gigantism appeared.

As to acromegaly, which is as a rule caused by an adenoma of the anterior portion of the hypophysis, developing from the eosinophilic elements, we have to suppose that the blood stream receives an abundance of a chemically abnormal secretion. This may have been the cause of changes in the patient's organism that led to acromegaly. Of course, this is a mere hypothesis.

It may be in place now to mention the classification of gigantism by Launnois and Roy. They divide this disorder according to its pathology into two kinds:

(1) Acromegalic gigantism, the result of hyperfunction of the anterior portion of the hypophysis;

(2) Eunuchoid gigantism or infantile gigantism in which

primary hypogonadism leads to the secondary hyperpituitarism.

Falta finds it quite difficult to give a clear, characteristic description of gigantism. This carefulness is fully justified, because after all, we know only that gigantism and acromegaly are related to each other but are far from being identical. As is generally accepted now, acromegaly results from adenoma of the eosinophilic elements in the anterior portion of the hypophysis, while there are other changes in the hypophysis that are limited to hyperplasia of the cellular elements that may lead to gigantism.

This would also explain the frequency of anomalies in the eyes in acromegaly: the failure of the eyesight, due to pressure exerted upon the optic nerve; the limited visual field (temporal hemianopsia) while these eye symptoms are only rarely observed in gigantism. In our case there is also the absence of any eye symptoms. It is possible, however, that in time the present clinical picture may radically change towards a larger degree of acromegaly.

As to therapeutic measures in gigantism, we consider it a disease that requires treatment, especially when, as in our case, the acromegalic stigmata appear. There was hardly any need of symptomatic treatment in our case, as there was an entire absence of the usual complaints in acromegaly—of headaches, rheumatic pains, etc. Again there was no indication for organotherapy, which in this case would be the preparations from the sexual glands. There was also no necessity for any operative interference, there being no reason to believe in the presence of a tumor in the hypophysis. Thus the only thing left to us was roentgenotherapy. As the patient presented undoubted symptoms of acromegaly, it is most likely that the supposed hyperplasia of the anterior portion of the hypophysis had already begun to acquire an adenomatous character. Hence the atrophic influence of the roentgen rays seemed to us the proper therapeutic agent. The treatment was given under direct supervision of Dr. Eisenstein. The patient received a full erythema dose.

Gramegna in 1909 was the first successfully to employ roentgenotherapy. Then in 1913 Béclère and other roentgenologists followed. Steiger collected 20 cases up to 1920, in

which roentgenotherapy was employed. In 1922, Kontschalowsky and Eisenstein also used this method with good results in treating acromegaly. The eye symptoms improved rapidly. This prompted us to apply the same method of treatment in our case as an *ultimum refugium* in the hope that we may at least check the acromegalization of our giant.

The results the future will show.

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STUDIES OF THE THYROID APPARATUS. XXX. THE RELATION BETWEEN AGE AT INITIATION OF AND RESPONSE OF BODY GROWTH TO THYROID AND PARATHYROID DEFICIENCY

FREDERICK S. HAMMETT

The Wistar Institute of Anatomy and Biology

PHILADELPHIA

INTRODUCTION

The time has now come when it is possible to gather together and interpret in orderly fashion the accumulated data of nearly six years of experimentation designed to make possible an evaluation of the part played by the thyroid and parathyroid glands in the growth of the mammal. A continuous supply of material (Mus norvegicus albinus) of uniform history kept under uniform conditions of diet and environment (1) has made possible a comprehensive study of this problem, in which is included a determination of the relative importance at different stages of development of the functions mediated by these glands in growth; a determination of the sex differences in growth response to their deficiency; and a determination of the differential growth sensitivity of the various organs to thyroid and parathyroid lack.

Previous papers of this series, in which the results of thyro-parathyroidectomy and parathyroidectomy at 75 and 100 days of age have been discussed, give the scope of the investigation, the mode of procedure, the methods of analysis, and the criteria used in determining the success of the operative technique. The numerical distribution of the animals according to age at time of operation, type of operation, sex and controls is to be found in the twenty-ninth paper of the series (2). This paper deals with the relative growth of the body in weight and length and the tail in length of the male and female albino rats subsequent to the glandular removals at the different ages (23, 30, 50, 65, 75 and 100 days).

In table 1 are given the initial and terminal mean values

TABLE 1

Age	Observed Mean Values of Body Weight, Body Length and Tail Length								
	Thyroparathyroidectomized					Parathyroidectomized			
Series	At Beginning			At End		At Beginning		At End	
	Ref. Conts.	Controls	Tests	Controls	Tests	Controls	Tests	Controls	Tests
MALES—BODY WEIGHT									
	g.	g.	g.	g.	g.	g.	g.	g.	g.
23	27.3±0.6	30.2±1.3	30.1±1.2	271.3±9.0	192.6±9.2	28.1±1.1	27.2±1.2	275.0±7.8	181.7±4.5
30	41.4±0.8	40.0±1.6	39.8±1.1	264.3±6.1	170.4±8.5	41.7±0.9	43.3±0.9	281.9±5.4	202.9±6.6
50	74.5±1.8	77.6±3.4	80.7±2.7	255.2±8.4	174.6±7.9	78.5±3.4	78.1±2.3	258.7±7.4	184.3±5.7
65	120.8±2.1	112.2±3.5	119.8±4.3	267.0±6.7	175.6±6.8	121.6±3.0	122.7±2.7	281.9±6.8	169.3±8.9
75	133.2±3.2	133.8±3.8	137.2±5.3	246.0±7.6	183.1±10.1	139.9±6.8	132.0±5.9	257.0±7.8	147.2±7.6
100	162.3±4.6	163.8±6.2	160.0±7.4	229.8±5.3	180.0±7.0	163.8±6.2	156.7±6.8	229.8±5.3	192.8±6.0
MALES—BODY LENGTH									
	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.
23	95.3±0.7	100.8±1.4	98.0±1.3	211.0±3.3	185.6±2.6	97.8±1.6	95.0±1.8	213.6±2.1	185.6±1.7
30	116.1±0.8	113.6±1.3	111.9±1.4	214.3±1.8	179.2±2.9	115.3±0.9	114.9±0.7	218.4±1.2	191.4±2.0
50	143.2±0.6	139.4±2.0	138.3±1.6	207.4±2.3	180.4±3.6	140.2±1.8	137.4±1.7	209.4±1.6	186.4±1.4
65	169.3±1.2	161.1±1.9	163.2±2.2	211.2±1.6	185.3±1.5	163.9±1.3	164.6±1.3	214.3±0.9	186.9±2.1
75	174.8±1.2	167.5±2.2	169.8±2.6	206.4±2.4	186.7±2.3	171.1±2.9	167.7±2.6	208.4±2.1	182.2±2.3
100	182.5±1.6	180.0±2.1	178.7±2.8	202.5±1.1	186.5±2.0	180.0±2.1	175.8±2.5	202.5±1.1	189.9±1.6
MALES—TAIL LENGTH									
	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.
23	67.4±0.8	70.7±1.2	70.2±1.5	180.8±3.6	153.4±2.0	70.4±1.3	68.3±1.7	187.4±1.8	161.3±2.0
30	85.7±1.0	87.0±1.5	84.0±1.6	187.9±1.2	149.4±3.5	87.1±1.1	86.7±1.3	189.6±1.1	165.9±1.8
50	119.3±1.9	121.0±2.1	122.5±1.6	182.1±1.4	154.3±3.2	119.2±2.3	122.3±1.3	181.8±1.0	165.1±1.5
65	145.1±1.3	134.9±1.9	141.5±2.1	175.9±1.3	157.0±1.3	144.0±2.3	143.8±1.2	182.1±1.2	164.3±1.6
75	146.4±1.2	144.6±2.0	148.3±1.9	173.9±1.7	159.9±1.7	151.6±2.7	147.2±2.1	178.1±1.9	159.1±2.1
100	155.9±1.9	158.6±2.2	154.3±2.4	172.2±1.4	159.3±2.3	158.6±2.2	155.3±2.0	172.2±1.4	163.9±1.9

TABLE 1—Continued

Age	Observed Mean Values of Body Weight, Body Length and Tail Length								
	Thyroparathyroidectomized					Parathyroidectomized			
Series	At Beginning			At End		At Beginning		At End	
	Ref. Conts.	Controls	Tests	Controls	Tests	Controls	Tests	Controls	Tests
FEMALES—BODY WEIGHT									
	g.	g.	g.	g.	g.	g.	g.	g.	g.
23	28.5±0.7	27.3±0.9	26.2±0.8	192.8±1.6	135.6±6.6	31.4±1.2	30.2±1.0	195.0±3.1	142.0±5.3
30	38.7±0.7	37.2±1.1	36.4±1.4	193.7±3.5	122.8±4.1	40.2±1.4	39.4±1.1	189.8±3.9	159.6±3.2
50	74.2±0.8	75.7±3.7	74.2±3.0	172.1±3.6	115.9±5.6	79.8±2.7	76.7±2.1	176.7±2.5	135.6±4.0
65	105.0±1.6	106.6±3.2	100.3±3.9	181.1±2.9	138.1±6.8	107:7±2.4	101.5±2.1	182.6±2.8	139.6±5.7
75	115.8±2.6	117.3±4.0	112.6±5.0	178.5±3.4	123.0±6.4	109.5±3.1	114.4±2.8	168.5±5.6	132.9±5.4
100	137.6±2.2	141.5±3.9	140.8±3.7	177.0±4.3	130.8±4.2	141.5±3.9	137.0±4.9	177.0±4.3	144.1±4.4
FEMALES—BODY LENGTH									
	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.
23	98.9±0.8	95.7±1.0	93.8±0.9	193.4±0.6	165.5±2.8	99.0±1.0	97.8±0.8	194.6±1.2	171.3±2.0
30	110.8±0.6	108.9±1.4	107.8±1.5	194.3±1.2	162.6±1.7	110.9±1.3	108.9±1.2	193.7±1.5	179.2±1.0
50	141.8±1.0	136.4±2.4	136.0±2.0	189.7±1.1	161.5±1.5	141.5±1.7	139.3±1.3	189.8±1.0	171.5±1.5
65	161.8±0.9	157.4±1.2	152.8±1.9	190.6±1.0	171.5±1.9	158.1±1.1	155.0±1.2	192.1±1.0	176.1±2.1
75	166.8±1.3	161.6±1.8	159.4±2.5	189.4±0.9	170.9±1.9	158.5±1.4	158.8±1.5	185.5±1.6	172.3±2.0
100	177.1±0.9	171.5±1.5	171.5±1.7	190.2±1.3	176.0±1.4	171.5±1.5	168.9±2.0	190.2±1.3	177.5±1.8
FEMALES—TAIL LENGTH									
	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.
23	74.3±0.6	69.3±0.7	66.5±1.4	170.2±0.9	138.2±3.7	73.5±0.7	71.7±0.7	170.1±1.7	154.3±1.6
30	86.3±1.1	84.9±1.1	83.4±1.4	166.7±2.5	138.8±2.0	89.3±1.9	88.9±1.5	169.8±2.7	161.8±1.2
50	120.0±1.7	122.7±3.3	119.7±2.4	167.7±2.4	140.8±1.3	126.3±2.3	123.5±1.5	170.0±1.3	154.3±1.6
65	141.1±1.7	139.8±1.6	137.0±2.2	165.0±1.1	145.4±1.6	141.7±1.6	139.6±1.7	167.6±1.0	157.5±1.8
75	143.9±1.1	146.7±2.3	147.4±2.5	163.2±1.4	152.4±2.0	145.0±0.9	148.6±1.4	162.1±0.7	159.7±1.5
100	152.6±1.3	153.3±1.2	154.5±1.1	163.5±1.3	156.6±1.1	153.3±1.2	152.3±1.9	163.5±1.3	157.3±1.8

The "Beginning" values are those observed at the ages given in the first column: the "End" values those observed at 150 days of age, the end of the period of observation for all groups.

TABLE 2
The Absolute and Relative Percentage Growth in Body Weight, Body Length and Tail Length.

Age Series	Thypars			Parathys		
	Conts.	Tests	T/C	Conts.	Tests	T/C
MALES BODY WEIGHT						
23	798.34	539.87	67.6	878.65	568.01	64.6
30	560.75	328.14	58.5	576.02	368.59	64.0
50	228.87	116.36	50.8	229.55	135.98	59.2
65	137.97	46.58	33.8	131.83	37.98	28.8
75	83.86	33.45	39.9	83.70	11.52	13.8
100	40.29	12.50	31.0	40.29	23.04	57.2
MALES BODY LENGTH						
23	109.32	89.39	81.8	118.40	95.37	80.5
30	88.64	60.14	67.8	89.42	66.58	74.5
50	48.78	30.44	62.4	49.36	35.66	72.2
65	31.10	13.54	43.5	30.75	13.55	44.1
75	23.22	9.95	42.9	21.80	8.65	39.7
100	12.50	4.36	34.9	12.50	8.02	64.2
MALES TAIL LENGTH						
23	155.73	118.52	76.1	166.19	136.16	81.9
30	115.98	77.86	67.1	117.68	91.35	77.6
50	50.50	25.96	51.4	52.52	35.00	66.6
65	30.39	10.95	36.0	26.46	14.26	53.9
75	20.26	7.82	38.6	17.48	8.08	46.2
100	8.58	3.24	37.8	8.58	5.54	64.6
FEMALES BODY WEIGHT						
23	606.23	417.56	68.9	521.02	370.20	71.1
30	420.70	237.36	56.4	372.13	305.08	82.0
50	127.34	56.20	44.1	121.43	76.79	63.2
65	69.89	37.59	53.8	69.55	37.54	54.0
75	52.17	9.24	17.7	53.88	16.17	30.0
100	25.09	—7.11	—28.3	25.09	5.18	20.6
FEMALES BODY LENGTH						
23	102.09	76.44	74.9	96.57	75.15	77.8
30	78.42	50.83	64.8	74.66	64.55	86.5
50	39.08	18.75	48.0	34.13	23.12	67.7
65	21.09	12.24	58.0	21.51	13.61	63.3
75	17.20	7.21	41.9	17.03	8.50	49.9
100	10.90	2.62	24.0	10.90	5.09	46.7
FEMALES TAIL LENGTH						
23	145.60	107.82	74.1	131.43	115.20	87.7
30	96.35	66.43	68.9	90.15	82.00	91.0
50	36.67	17.63	48.1	34.60	24.94	72.1
65	18.03	6.13	34.0	18.28	12.82	70.1
75	11.25	3.39	30.1	11.79	7.47	63.4
100	6.65	1.36	20.5	6.65	3.28	49.3

for the various groups of the several age series, together with their probable errors. In table 2 are given the absolute percentage increments and the relative increments of the tests in terms of those of their controls, the values being derived from the data in table 1. In order to facilitate analysis by visualization the relative values have been charted. Chart 1 shows the sex differences, chart 2 the differences in body weight, body length and tail length, and chart 3 the differences in response to the two types of glandular deficiency.

AGE DIFFERENCES

It is clear from both tables and charts that growth in body weight, body length and tail length of both sexes is retarded by the production of a thyroid or parathyroid deficiency at each of the stated ages. I shall consider the retardation following thyro-parathyroidectomy as an expression of a reaction to *thyroid* deficiency for the reasons which have been given in the preceding paper (2). The retardation following parathyroidectomy is obviously attributable to a parathyroid deficiency (3).

From charts 1 and 2 it is at once evident that the degree of growth retardation in body weight, body length and tail length in both sexes subsequent to the initiation of a thyroid deficiency increases with the age of the animal at the time of glandular removal. The older the animal the more it is dependent upon thyroid function for normal growth. This was indicated in an earlier study and is now confirmed and established (4). The detailed explanation of the phenomenon with respect to growth in body weight has been given in the preceding paper (2) and need not be repeated. The principle is extensible to growth in body and tail length. It is based on the well known fact, which needs no demonstration, that the normal rate of growth decreases with advancing age, and the fact that growth by increase in cell mass becomes with increasing age progressively a greater proportion of total growth while growth by increase in cell number becomes progressively a smaller proportion. In this shift in ratio the importance of the thyroid in growth increases with the increase in proportion of growth by increase in cell mass, because the role of this gland in growth is that of a participant in the regulation of

the metabolic level, through which is determined the rate of the maintenance processes of the organism and hence the amount of material presented to the cells for growth purposes during a given period. Hence the older the animal the more it is dependent on thyroid function for normal growth.

Now although the generalization given above that the direction of change in degree of retardation increases with increasing age at the time of thyroid removal is valid, an inspection of charts 1 and 2 shows that the course of the progression is divisible into two periods; the period before and the period after the incidence of puberty (from 23 to 65 and from 65 to 100 days of age). Up to and including the 65-day-old series

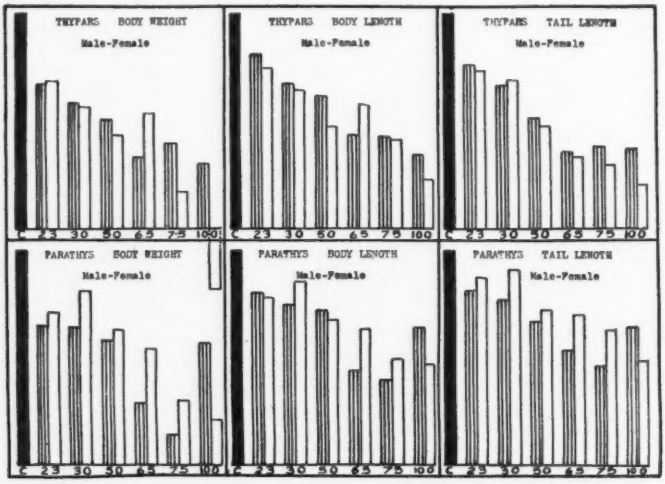

Chart 1. The growth in body weight, body length and tail length of the test groups in terms of that of their controls arranged for sex comparison.

the increase, in the males, is consistent and marked; while from 65 days on the degree of change is quantitatively negligible, though of course directionally significant. Puberty has evidently introduced a new factor conditioning the degree of response to thyroid deficiency in both sexes and which in the males tends towards stabilization. This tendency at this stage of development has been noted in bone growth and differentiation (5) (6) (7) (8) and in the course of growth in body weight

of these thyroidless rats of the 23, 30, and 50-day-old series (2). In the females, puberty conditions a different type of response, viz., an increase in resistance to thyroid deficiency initiated at 65 days of age as compared with the reaction of the 50-day-old group; while the retardation in the 75 and 100-day-old groups is markedly and progressively greater instead of tending towards stabilization. While these sex differences in details exist, they do not becloud the principle of a pubertal modification of growth response to thyroid deficiency.

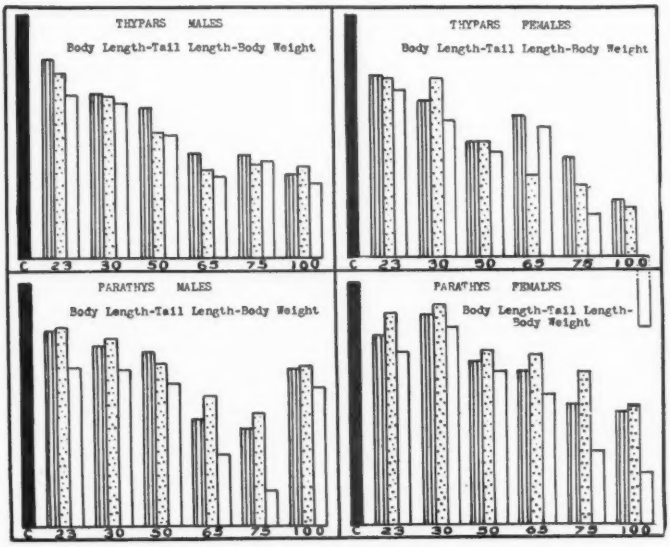
THYPARS MALES
Body Length-Tail Length-Body Weight
C 23 30 50 65 75 100
THYPARS FEMALES
Body Length-Tail Length-Body Weight
C 23 30 50 65 75 100
PARATHYS MALES
Body Length-Tail Length-Body Weight
C 23 30 50 65 75 100
PARATHYS FEMALES
Body Length-Tail Length-Body Weight
C 23 30 50 65 75 100

Chart 2. The growth of the various test groups in terms of that of their controls arranged for comparison of body weight, body length and tail length.

Turning now to the parathyroidless groups it is seen from charts 1 and 2 that increasing age at time of glandular removal conditions in general an increasing subsequent growth retardation in body weight, body length and tail length. This progression indicates a fundamental similarity in organic reaction to both types of glandular deficiency. The relation has been analyzed and discussed in the previous paper (2). It is based on the idea that growth retardation following parathyroid removal is largely attributable to a lowering of the nutrient level

because of a disturbance in the effectiveness of the digestive system. Combined with this there is, of course, the increased maintenance utilization of metabolites caused by the mild but chronic tetany.

The increase in gross growth retardation with increasing age at time of initiation of the parathyroid deficiency is explicable on the basis of the interaction of these two phenomena. For as the growing animal becomes older it uses a progressively lesser proportion of metabolites for growth and a progressively larger proportion for maintenance. Hence a restriction of the available nutrients combined with a relative increase in the de-

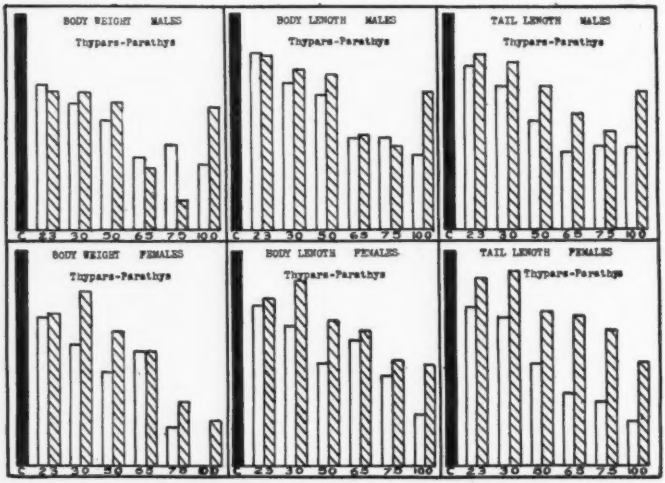

Chart 3. The growth in body weight, body length and tail length of the tests in terms of that of their controls arranged for comparison of the response to thyroid and parathyroid deficiency.

mand on the part of the maintenance processes would of necessity cause a progressively greater than normal reduction in the proportion of materials used for growth purposes with increasing age of the animal at the time of the initiation of the metabolic disturbance; an expression of which would be a progressive increase in general growth retardation.

This interpretation fits the observations. Others that suggest themselves are incomplete or not in accord with the facts. For instance it might be said that the phenomenon is an ex-

pression of an increasing sensitivity to the toxemia as such. This explanation fails to take into account the fact that older animals are less susceptible than younger to death from tetania parathyreopriva. It might be said that since the metabolic rate of young animals is greater than that of older, the disposal of toxic products is more easily effected and hence growth is less retarded. But if we assume, as I believe it just to do, that the toxic products are endogenously produced, it is obvious that these would be formed in larger relative amount in the younger more metabolically active animals and hence growth would be retarded to an equal or greater degree than in the older groups. Moreover, the younger test groups (23, 30 and 50-day-old series) as they grow older presumably decrease in metabolic activity, yet they fail to exhibit any decrease in percentage rate of growth different from that which normally occurs with age (2). This they would be expected to do if the interpretation was adequate. Finally, it might be said, as has been done in earlier papers, that the reaction is due to the progressive decrease with age in the growth capacity which is inherent in the organism as a collection of living cellular units, and that the urge to grow being weaker it is the more susceptible to blocking by adverse conditions. Such an entlechlical interpretation is merely a begging of the question and only useful as a tentative point of view.

The interpretation that is acceptable is consistent with the facts. It of course differs from that given for the age reaction to thyroid deficiency because the primary disturbance is different. It is, however, consistent with the idea developed in the preceding paper (2) that the growth retardation of parathyroid deficiency is immediately largely conditioned by a situation essentially the same as that existing in thyroid deficiency (e. g. a decrease in the amount of materials available for growth): and with the complementary idea that the mechanism of growth adjustment to the two types of glandular deficiency is also essentially the same.

That puberty is a factor conditioning the degree of growth retardation to parathyroid deficiency in the males in body weight and length, and in the females in body weight is shown on charts 1 and 2 by the abrupt decrease which occurs in the relative per cent growth of the tests at this time. That this

effect is apparently restricted in the males to this period, following which the retardation becomes approximately the same as before, is an inexplicable anomaly which, however, does not detract from the validity of the generalization. The significance of the phenomenon has been discussed elsewhere (2). Attention is called to it here as it will be in future papers in order to attest its ubiquitousness. That it is real and differential in its influence will be shown.

SEX DIFFERENCES

Now the direction of the sex difference in degree of growth retardation in body weight, body length and tail length, due to thyroid deficiency, is correlated with the direction of sex difference in normal growth rate and on the same course as that which occurs with age. That is to say, just as the degree of retardation is greater the less the rate of normal growth on age; so is the degree of retardation greater in the females of normal lesser rate of growth than the males. This is what is to be expected if the interpretation of the age differences is well founded. Its occurrence is, therefore, consistent with and confirmatory of the conception (2).

Parathyroid deficiency, on the other hand, results in a greater growth retardation in body weight, body length and tail length in the male than in the female. This reversal of direction of sex difference is not a breach in the validity of the interpretation, as it might be considered at first sight.

The sex difference in degree of retardation is conceivably due to the sex difference in the degree to which the nutrient level is reduced. This is directly due to the sex difference in sensitivity to the toxemia of the parathyroid deficiency. That is to say, in the case of parathyroid removal, growth retardation is secondary to a toxemia. Sex specific factors determine the primary response from which the subsequent growth reaction is conditioned. In the case of thyroid removal, however, this supplementary influence is absent and the sex difference in response is determined by the inherent sex difference in normal growth rate and the relation of thyroid activity thereto.

On the basis of what has gone before it would be expected that the puberty effect would be more marked in the sex which is the more sensitive to the particular glandular deficiency. Such is found to be the case as can be seen from chart 1. The

change in degree of growth retardation occasioned by thyroid removal at the attainment of sexual maturity is more marked in body weight and body length in the females than in the males. In the parathyroidless groups, on the other hand, it is the males that are more seriously affected, the females showing little if any alteration from the normal progressive decrease with age. The consistency of these interrelations with the basic assumptions is gratifying.

BODY WEIGHT, BODY LENGTH AND TAIL LENGTH DIFFERENCES

The values in table 2 show that the relative degree of growth retardation in body weight, body length and tail length subsequent to glandular removal, bears no consistent relation to the relative degree of normal growth. This is what is to be expected since the growth processes concerned are presumably qualitatively as well as quantitatively different (9).

From chart 2 it is seen that growth in body weight is consistently more retarded by both types of glandular deficiency than is growth in body length and tail length. As a result the test animal becomes more rangey than the normal. This shift in bodily proportions is like that which occurs in conditions of defective nutrition (10). The similarity indicates that the interpretation of the growth response to the glandular defects in terms of decrease in materials available for growth is well taken.

In a previous paper (11) the assumption was made that growth in body weight is more representative of growth by increase in cell mass, while growth in body (or tail) length is more representative of growth by increase in cell number. A strict delimitation of the two phases is obviously not intended in this broad generalization. Evidence that growth of the axial skeleton of the albino rat by increase in cell number persists for a considerable time after birth, even up to the age when body growth in weight is almost exclusively a matter of increments in cell mass is had from a recent paper by Strong (12). Hence assumption is not inconsistent with observation.

On the basis of this differentiation the conclusion was drawn that growth by increase in cell mass is more sensitive to inhibition by thyroid and parathyroid deficiency than is growth by increase in cell number. The analysis given in the preceding paper (2) and the observations reported by Jackson (10) sub-

stantiate and extend the deduction, respectively, so that the following biological principle can be stated: *Growth by increase in cell mass is more sensitive to inhibition by a diminution in the materials available for growth, than is growth by increase in cell number.* An expansion of the concept would be interesting but this is hardly the place therefor.

There is a very evident tendency for growth in tail length to be more retarded than growth in body length by thyroid deficiency. On the other hand growth in body length tends to be more retarded than growth in tail length by parathyroid deficiency.

This difference in the direction of difference might seem to be a stumbling block to the general validity of the growth retardation were it not for the fact that we are here dealing with structures, important components of which are peculiarly related to a phase of metabolism in direct relation to an apparently specific function of one of the glands being studied. I refer to the vertebrae in their relation, as bones, to calcium metabolism and the function of the parathyroids in its relation to the same process. Under conditions of parathyroid deficiency in which, on a retardation due to lowering of the general nutrient level there is superimposed a retardation (specific for bone growth) due to a specific diminution of available calcium, it is not to be expected that the relative growth of the vertebrae of the tail as compared with those of the body would be the same either in degree or in direction as under conditions where the specific defect of specific importance to bone growth is lacking or at least much less marked as is the case in thyroid deficiency (13). It is not to be expected because each group of vertebrae obviously has its own distinctive type of metabolism with its own relation to growth, and hence its own type of response to the specific and non-specific metabolic defect which in turn must participate in the determination of the relative degree of response to the different conditions. This phase has already been discussed as noted earlier (9).

DIFFERENCES IN RESPONSE TO THE TWO TYPES OF GLANDULAR DEFICIENCY

From chart 3 it is seen that the degree of retardation of growth in body weight, body length and tail length is generally

less in parathyroid than in thyroid deficiency. It is less in the former than in the latter because the decrease in material available for growth is less. It must not be overlooked, however, that this decrease is a consequence of a distortion of cell activity, in the one case by a toxemia, in the other by a lowering of the metabolic level, and that the former is presumably largely mediated through a specific action on the nervous system and is hence restricted, while the latter is general and on the basic processes common to all living cells.

Now it has been pointed out that the degree of retardation increases with the age at which the glandular deficiency is initiated. It will be noted from chart 3 that the extent of this decrease is greater in the case of thyroid than in the case of parathyroid deficiency. This relation is in accord with the interpretation of the age difference in degree of response and is another example of the interdigitation of observation and theory.

The influence of puberty in bringing out a differential response is shown in the body weight and body length values. The effect is more marked in the males than in the females.

In general the difference in degree of response to the two types of glandular deficiency is greater in the female than in the male. This is because the female is less retarded than the male by parathyroid deficiency and tends to be more retarded by thyroid deficiency. This difference has been interpreted in an earlier paragraph. The difference is more marked in the tail length relations, which fact is consistent with the idea of Przibram (14) that tail length is a facultative tertiary sex characteristic in the rat. If the hypothesis is correct it is of importance to students of the incretory organs.

SUMMARY

In the foregoing pages I have pointed out and interpreted the salient sex and systemic similarities and differences in growth response to thyroid and parathyroid deficiency initiated at different stages of development in the life of the albino rat in so far as growth in body weight, body length and tail length is concerned. The agreement of the findings with the principles developed from a study of the course of growth of these same animals is good, and an indication of their essential validity.

The following are the significant points from which the interpretations and conclusions found in the text are derived:

1. The older the animal at the time of the initiation of the glandular deficiency the greater the subsequent retardation of growth in body weight, body length and tail length.

2. Puberty is a significant factor in the determination of the growth response to thyroid and parathyroid deficiency.

3. Growth of the male is less dependent on the functions mediated by the thyroid than is growth in the female.

4. Growth of the male is more retarded by parathyroid deficiency than is that of the female.

5. Growth in body weight is more retarded than growth in body length or tail length.

6. Growth is more retarded by thyroid than by parathyroid deficiency.

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STUDIES ON THE OESTROUS CYCLE IN THE RAT. II. THE EFFECT OF THYROPARATHYROIDECTOMY AND PARATHYROIDECTOMY

MILTON O. LEE

From the Department of Physiology, Ohio State University
COLUMBUS

The effect of thyroidectomy on the oestrous cycle in the female albino rat was reported in a previous paper (Lee, 1925). The length and character of the oestrous cycle, as determined by the vaginal smear method, was used as an index of ovarian activity, thus affording what is believed to be an accurate objective method of studying the supposed intimate relationship between the thyroid and ovary. The effect obtained was an average lengthening of the cycles in thyroidectomized animals of about one day over cycles in normal controls (5.9 and 4.8 days respectively). This lengthening of the oestrual rhythm is conceivably due to the loss of the direct stimulating influence of the thyroid on the ovary, or more likely to the lowering of the general level of metabolism in the animal.

Using reproductive ability and the growth of the reproductive organs as an index of the inter-relationship of thyroid and ovary, Hammett (1922, b; 1924) has concluded that parathyroidectomy and thyroparathyroidectomy have no direct effect on the reproductive system, but an indirect one due to the lowering of the metabolic level of the organism and resulting in a condition of partial physiological inanition. That ovarian activity is closely conditioned by the general well-being of the animal is a fact reported by several workers (Evans and Bishop, 1922; Papanicolaou and Stockard, 1920) and attested by numerous experiences in this laboratory. Any condition of loss of weight, infection, undernutrition, crowding of animals in small cages, or extreme variations in temperature, is quickly reflected in a prolonged dioestrum interval in the oestrous cycle.

The use of the length and character of the oestrous cycle as an index of ovarian activity is regarded as being well adapted to these particular problems. The vaginal smear method of

following the cycle in the rat, developed by Stockard and Papanicolaou (1917) and by Long and Evans (1922), affords an easy means of following cycle after cycle of ovarian activity without interfering with the process to any significant extent. For example, in the three series of 57 rats reported in this paper, 1836 cycles, involving a total of 9904 days or more than 27 years, were followed in a course of six months. Since any method of studying inter-relationships of endocrine glands is essentially a statistical one, the advantages of a method giving a large mass of data are apparent at once. To obtain an equivalent number of data by the use of reproductive ability as an index, for example, would require either many times the number of animals, or that the observations be carried on over a period of years.

MATERIAL AND METHODS

Eighty-four female albino rats of from 100 to 150 days were used in these series. Twenty-three of these served as controls, and were also used as controls for the thyroidectomized series reported upon previously. Parathyroidectomy was performed upon twenty animals and thyroparathyroidectomy upon forty-one others. Of these, thirteen rats died after the operation, seven developed poor health during the course of the experiment and were discarded, while seven others were found at autopsy or biopsy to have regenerated some thyroid or parathyroid tissue. These also were discarded from the groups. Five of the control series were subjected to a sham operation to determine the effect of trauma on the cycles. Later in the experiment the incisor teeth of these five animals were kept short, as a check on a similar condition in the parathyroidectomized animals.

The environmental conditions, food, housing arrangements, etc., are described in detail in the previous paper and need not be repeated here. It should be emphasized possibly that the ration was rich in calcium (1.5% $CaCO_3$).

In the removal of the thyroids and parathyroids the following technic was used. The animal was maintained under ether anesthesia and tied out, back down, on a small board under a binocular microscope. After exposure of the tissues in the neck,

fine silk ligatures were placed around the vessels entering each thyroid lobe at the anterior and posterior ends, care being taken that all of the thyroid and parathyroid tissue lay between the two ligatures. The mass of thyroid and parathyroid tissue was then grasped by fine forceps and carefully teased out with a flexible needle. Histological examination was made of all tissues removed, to make sure that both parathyroids were actually ablated. One animal in which the extirpated thyroids contained only one parathyroid was discarded from this series and placed in the thyroidectomized series.

In the removal of the parathyroids alone, essentially the same general technic was followed except that ligatures were placed only at the anterior poles of the thyroids. From each lobe a small amount of thyroid tissue (not over one-fourth of the gland) containing the parathyroid was then removed. In some cases the parathyroid was so prominent that it could be easily cut cleanly away from the surrounding thyroid. In actual practice it was not decided which glands of a particular animal were to be removed until the neck tissues were exposed. Then in case the parathyroids were plainly visible under the capsule at the anterior poles of the thyroids, they alone were removed and the animal was placed in the parathyroidectomized series. In case the parathyroids were embedded deeply in the thyroid and not visible from the surface, both glands were removed and the animal was placed in the thyroparathyroidectomized series.

The mortality from the operations was fairly low, 20 per cent of the thyroparathyroidectomized, and 20 per cent of the parathyroidectomized animals dying. It has been shown by various workers (Boothby, 1921; Islein, 1908) that complete parathyroidectomy is not always fatal in the rat, and Hammett (1921) has shown that the extent to which the animals have been "gentled" has much to do with the percentage of survivals.

At the end of the observation period all of the experimental animals were autopsied or biopsied, as a check on the completeness of the operation. From the thyroparathyroidectomized series all suspected tissues was removed and sectioned. Of the thirty animals, three showed some regeneration of thyroid tissue and one showed some parathyroid tissue which had either not been removed or which had regenerated. These rats were dis-

TABLE 1

Showing Lengths of Oestrous Cycles, in Order of Occurrence, in Control Series

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS
275	5,6,4,4,5,4,5,5,4,4,5,5,7,6,4,6,5,6,4,5,4,5,5,5,4,4,5,5,4,5,5,4,5,5,6,5,5,5,4,5,4,5,4,5,4,4,4,5,5,4,5,5,4,5,5,5	52	249	4.8
276	6,5,5,5,6,5,5,5,4,4,5,6,5,4,4,5,6,5,4,5,5,5,5,4,5,5,5,4,5,5,6,5,4,5,5,5,5,4,5,5,5,5,5,5,5,4,5,5,5,5	49	240	4.9
222	5,5,6,5,4,4,5,5,6,4,4,5,4,5,6,4,5,5,4,5,6,5,5,5,4,4,5,4,5,5,5,4,6,6,4,5,5,5,4,5,5,6,4,5,5,5,4,5,5,5,4	51	246	4.8
284	5,6,4,5,6,6,5,4,5,6,5,5,5,4,4,6,7,5,5,5,6,5,5,5,5,5,5,5,4,5,5,5,5,4,5,5,5,5,4,6,5,5,4,5,4,5,4,6,4,5,5	49	245	5.0
287	5,4,6,4,5,6,5,4,5,5,4,4,5,5,4,5,5,6,5,4,4,5,5,5,5,5,5,4,5,5,6,6,7,5,5,5,4,5,5,4,5,4,5,5,5,4,5,4,5,5,5	51	248	4.9
288	5,4,5,5,5,4,6,5,5,4,4,5,5,5,5,5,5,5,4,4,5,5,5,5,4,5,5,5,5,5,4,5,6,4,5,4,5,5,4,4,5,6,5,5,4,5,5,5,6,5,4,5	52	250	4.8
297	5,6,5,6,4,4,6,4,6,5,5,4,5,5,5,5,5,5,6,4,4,5,5,5,4,5,4,5,4,5,5,5,4,5,5,5,5,4,5,5,5,4,5,5,5,5,5,4,4,5	50	241	4.8
298	4,5,5,4,5,5,5,5,4,4,5,5,5,4,4,5,5,5,4,4,5,5,5,4,5,5,6,5,5,5,5,6,5,5,4,4,5,5,5,5,5,6,4,5,4,5,5,5,4,5,6	51	245	4.8
413	4,4,5,6,5,4,5,5,6,4,5,4,4,4,4,5,5,5,5,5,5,5,4,5,5,4,5,5,5,5,5,5,5,5,5,5,4,4,5,5,4,5,4,4,4,5,5,5,5,6,5,5,5,5	51	244	4.8
564	5,4,5,5,5,4,4,6,4,5,5,5,5,5,5,6,5,5,5,5,7,5,4,5,4,5,5,5,5,6,4,5,4,5,5,4,5,5,5,5,5,5,5,5,5,4,4,5,5,5,4	50	243	4.9
565	5,6,6,5,7,5,4,5,6,4,5,4,5,5,5,5,4,5,5,4,5,5,5,6,5,5,5,5,5,5,5,4,5,4,5,4,5,5,5,5,5,5,5,5,5,4,5,5,6	49	243	4.9
566	6,4,6,6,5,5,5,5,4,5,5,5,5,4,5,5,4,5,5,4,5,5,5,5,5,4,5,5,5,4,5,5,4,5,5,4,5,5,5,5,4,5,5,5,5,4,4,5,5,5,5,5,6,5	51	248	4.9
586	4,4,5,4,4,5,5,5,5,4,5,5,5,4,4,5,5,5,6,6,5,4,4,6,5,4,4,4,5,5,5,4,5,5,5,5,5,4,5,5,5,4,5,5,4,5,5,5,4,5,6,5,4,5,4	52	246	4.7
587	5,5,5,5,5,4,5,5,5,5,4,4,4,5,5,5,5,5,4,5,5,5,5,4,4,5,5,5,4,5,6,4,5,4,5,4,4,5,4,5,5,5,6,4,5,4,5,6,4,5,5	51	242	4.7
588	5,5,5,5,5,4,4,5,5,5,5,4,5,5,5,4,4,5,5,5,5,5,5,6,4,5,5,5,6,4,4,5,5,5,5,5,4,5,5,4,5,5,5,5,5,5,4,5,4,5,5	51	245	4.8
	Totals	760	3,675	....
	Average	50.7	245	4.8
	Standard deviation	..	....	$\pm$0.1

carded from the series. From the parathyroidectomized animals all of the thyroid tissue left behind at the operation was removed and sectioned. In all of these cases there was abundant thyroid tissue present and in a few cases thyroid that had been left had apparently hypertrophied. In two cases some parathyroid tissue was found as small islands in the thyroid. These animals were discarded. Thus in the final series only those animals were included which were positively lacking the parathyroids or the thyroids and parathyroids, respectively.

In thirty-nine animals symptoms of parathyroid deficiency became apparent after the operation. The first symptom noted was the development of typical parathyroid tetany in twenty-one cases within two days after the removal of the glands. Eleven animals succumbed to the attacks, the remaining ten recovering and showing no further evidence of tetany. Tetany was not observed in twenty-seven animals, but it should be mentioned that they were under observation only a few hours each day. The second effect did not show until some time after the operation when, in most of the parathyroidectomized and in some of the thyroparathyroidectomized animals, the teeth began to show an overgrowth, becoming much longer, curved and curled as described by other observers (Hammett, 1922, a). In most cases the teeth also became brittle and soft, breaking easily at the level of the gum. As soon as this condition was noticed the teeth showing overgrowth were kept clipped to something like normal length. These rats showing abnormal teeth were often unable to gnaw or to eat hard food, and soft food (of the same composition as the baked ration of the other animals) had to be used. This ration was not always eaten readily and in some cases body weight was not maintained.

In order to determine just what effect this disturbance of the teeth and the subsequent partial inanition might have on the oestrual cycles, the condition was imitated in the five traumatized control rats, which had completely recovered from the effects of the sham operation. The incisor teeth of these animals were clipped just above the gum once a week, and soft food was fed. Bodily growth and weight were not maintained and the oestrual cycles became longer and more irregular, as may be seen from examination of Table 2.

TABLE 2

Showing Lengths of Oestrous Cycles in Traumatized Rats

RAT NO.	(A). LENGTHS IN DAYS OF SUCCESSIVE CYCLES AFTER SHAM OPERATION	SUMMARY (A) NO. OF CYCLES	SUMMARY (A) NO. OF DAYS	SUMMARY (A) AVERAGE LENGTH OF EACH CYCLE DAYS
347	*(8),(9),6,5,4,5,4,4,6,5,5,4,5,4.....	12	57	4.8
232	(10),4,5,5,4,4,7,5,4,4,6,5,5,5,4.....	14	67	4.8
205	6,5,5,6,4,5,5,4,8,4,5,5,4.....	13	66	5.1
168	(9),5,7,4,6,5,4,4,4,8,4,5,5.....	12	61	5.1
242	(11),6,7,4,4,5,5,3,6,5,4,5.....	11	54	4.9
	Totals.....	62	305	....
	Average length of cycle (days)....	..	..	4.9

RAT NO.	(B). LENGTHS OF CYCLES DURING PERIOD OF CLIPPING INCISOR TEETH	SUMMARY (B) NO. OF CYCLES	SUMMARY (B) NO. OF DAYS	SUMMARY (B) AVERAGE LENGTH OF EACH CYCLE DAYS
347	5,4,6,9,7,4,6,6,5.....	9	52	5.7
232	4,6,5,7,5,8,4,5.....	8	44	5.5
205	5,9,6,5,7,6,5,5,6.....	9	54	6.0
168	6,4,5,7,5,4,6,8.....	8	45	5.6
242	5,8,7,5,6,3,8,5.....	8	47	5.8
	Totals.....	42	242	....
	Average length of cycle (days)....	..	....	5.7

* Parentheses ( ) around numbers indicate lengthened cycles immediately following operation. These figures were not used in the calculations.

Daily determination of the stage of oestrous were made by the vaginal smear method, in the case of the control series from October to the following June, and in the case of the experimental animals from December to the following June. The experimental rats were operated upon in January, their oestrual cycles from the time of puberty up to the time of removal of the glands having been normal in length and character.

OBSERVATIONS AND DISCUSSION

In the control series of fifteen animals the cycles were within normal limits in length and character throughout the period of observation, indicating that environmental conditions were favorable. The total average length of cycle in these controls over a period of eight months was 4.8 days, a figure which differs but slightly from that found by Long and Evans (1922) in their colony. For the details of the cycles in these rats see Table 1. Four of the five traumatized control animals showed lengthened cycles immediately after the operation, followed by a return to normal length. Later, after clipping of the teeth began, the cycles became somewhat longer and more irregular (see Table 2). In the three rats which showed regeneration of the thyroids there was a return to cycles of nearly the same length as those of the controls.

The thyroparathyroidectomized series after discarding all rats showing regeneration, consisted of twenty-six animals, all of which had shown cycles of average normal length (4.9 days) before operation. Nineteen of these animals showed a disturbance of the oestrual rhythm immediately after the ablation of the glands, lasting from 9 to 35 days and involving one to three cycles (Table 3). This lengthening of the cycles is ascribed chiefly to operative injury and, in some cases, slight infection, since it is very similar to the condition in the traumatized control series. Seven of the parathyroidectomized rats showed a similar disturbance of the cycles after operation, although not so extensive as in these thyroparathyroidectomized animals. The trauma was undoubtedly more severe in this series from which both glands were removed, but there still remains the possibility that following thyroidectomy or thyroparathyroidectomy some endocrine adjustment may occur, and that only gradually as this adaptation takes place does the ovarian activ-

TABLE 3

Showing Lengths of Oestrous Cycles, in Order of Occurrence, in THYROPARATHYROIDECTOMIZED Rats

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF CYCLES DAYS
147	*(15),6,9,6,6,3,4,8,5,8,4,5,6,6,7,5,6,4,8,6,6,8,5,7,5,6,6,7,5	28	167	6.0
243	(5),(16),(10),8,7,6,5,8,7,8,7,9,5,7,7,5,5,6,6,6,5,5,4,6,5,5,6,4,4,6,5,5,7,4,5	32	188	5.9
248	6,6,11,5,4,8,5,6,5,5,8,7,7,5,5,9,5,5,7,6,4,9,6,5,5,10,6,4,6	29	180	6.2
495	(25),5,7,5,5,4,8,4,6,5,9,5,6,6,6,5,6,10,5,4,6,7,6,5,6,7,6,7,6,6,5,8	31	186	6.0
551	7,4,6,5,7,5,6,6,5,4,8,6,7,5,9,4,6,5,6,8,6,5,6,5,9,4,5,6	28	165	5.9
554	(8),(14),5,4,10,6,5,7,6,7,9,4,6,6,7,5,6,9,6,5,7,5,6,6,8,7,7,6,4,5,7,5	30	186	6.2
562	(16),(9),(10),6,4,6,5,5,6,5,7,5,6,3,6,6,6,5,7,8,5,5,5,4,5,7,6,6,5,6,7,8,6	30	171	5.7
577	(14),6,6,6,5,6,8,7,6,5,6,7,6,8,8,7,6,6,5,5,6,6,3,6,7,7,6,8,4,6	29	178	6.1
598	(16),8,5,9,6,5,5,7,4,5,6,8,6,6,5,4,9,7,6,6,7,6,8,5,6,7,8,7,5	28	174	6.2
610	(21),7,4,8,7,5,6,5,7,7,4,5,5,6,6,5,6,7,5,8,5,7,4,6,5,5,6,4,6,5	29	166	5.7
624	(9),(13),5,7,7,7,10,6,6,4,4,5,6,7,4,7,6,7,5,8,7,8,5,7,6	23	144	6.3
767	(19),7,4,6,9,7,7,9,6,5,6,5,6,6,5,5,6,5,5,6,7,3,9,4,5,6,8,7	27	164	6.1
768	7,8,7,5,6,6,6,7,7,8,8,5,7,6,6,7,8,6,6,5,8,5,6,5,7,5,7,6	28	180	6.4
770	6,5,9,8,8,4,5,7,6,8,6,7,4,6,5,8,6,5,4,6,7,6,5,9,5,6,4,6	28	171	6.1
780	(11),7,5,6,7,4,5,8,5,5,9,4,6,5,5,7,6,8,6,4,5,7,6,5,8,6,5,5,6	28	165	5.9
790	(9),(15),8,7,4,6,5,10,6,13,7,8,5,6,6,9,8,7,6,5,6,9,7	21	148	7.0

TABLE 3 (Continued)

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF CYCLES DAYS
853	(10),7,6,7,7,4,7,10,7,5,6,6,6,5,7,6,8,5,6,6,6,6,4,6,7,7,6,5	27	168	6.2
855	8,9,7,4,5,6,5,6,8,5,4,7,9,6,7,6,7,6,4,8,6,6,8,6	24	153	6.4
856	(14),8,6,4,7,9,6,4,6,5,7,5,8,5,6,7,5,7,6,8,5,6,4,5,5,6,7	26	157	6.0
857	(9),7,6,6,4,6,8,6,8,5,7,5,4,4,6,5,3,6,5,9,5,4,5,6,7,4,7,6,6,7	29	167	5.7
858	(10),4,8,6,8,5,6,5,4,8,5,7,6,6,5,7,5,7,6,8,4,5,5,4,8,6	25	148	5.9
859	7,6,5,6,5,7,9,6,4,5,7,5,7,6,4,6,8,4,6,4,7,6,6,5,7,6	26	154	5.9
863	(21),(11),7,5,5,4,6,6,7,6,5,5,4,6,5,6,5,6,5,6,5,6,6,6,6,7,6,5,8,7,6,6,5	31	178	5.7
870	(12),(14),(9),7,5,6,5,3,5,6,4,6,5,6,5,4,4,6,5,6,5,5,5,4,7,6,5,7,4	26	136	5.2
876	7,5,6,6,7,4,5,5,6,8,5,7,6,6,7,6,5,8,4,5,6,5,5,5,6,7	26	152	5.8
877	(12),7,8,4,6,5,6,6,4,5,8,5,5,9,5,6,7,4,6,5,7,7,6,5,6,7	25	149	5.9
	Totals	714	4295	....
	Average length of cycle	..	....	6.0
	Standard deviation	..	....	$\pm$0.3
	Coefficient of variation	..	....	5.0

* For explanation of symbols see **Table 2.**

TABLE 4

Showing Lengths of Oestrous Cycles, in Order of Occurrence, in PARATHYROIDECTOMIZED Rats

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS
187	*(12),(9),5,6,6,5,5,8,7,4,5,5,4,4,5,5,6,5,5,6,6,4,5	21	111	5.3
235	7,4,5,4,5,5,9,6,5,8,6,5,5,5,4,4,5,4,5,6,7,6,5,5,8,5	26	143	5.5
255	6,6,5,4,5,4,5,6,6,5,4,4,4,5,7,9,6,4,4,5,5,5,4,6,6,5,6	27	141	5.3
278	(13),6,6,4,4,5,6,9,4,5,6,6,5,5,5,4,5,4,4,5,10,6,5,5	23	124	5.4
290	6,5,5,4,7,10,6,4,4,5,4,5,6,6,5,5,5,8,7,5,5,4,4,6,5	25	136	5.4
299	(10),5,5,5,6,4,5,5,4,11,8,6,6,5,4,4,5,4,4,4,6,7,5,6,5	23	125	5.5
497	(7),(15),7,6,6,5,5,6,4,4,4,5,6,5,5,9,8,4,4,3,6,5,5,4	22	116	5.3
579	6,5,5,11,9,4,5,5,7,5,4,4,4,6,4,5,5,7,4,4,5,6,7,5	24	132	5.5
782	(9),(14),8,6,6,4,4,5,5,3,5,6,4,4,7,6,6,5,5,5,4,4,5,7	22	114	5.2
814	(18),8,6,5,5,5,6,4,4,5,4,8,12,6,4,4,5,6,5,5,5,4,5,6,8	24	135	5.6
816	(14),(11),(9),6,6,5,5,5,4,4,6,5,4,6,5,5,8,5,5,4,5,7,5,5	21	110	5.2
	Totals	258	1387	....
	Average length of cycle (days)	..	....	5.4
	Standard deviation	..	....	±0.1
	Coefficient of variation	..	....	1.9

* For explanation of symbols see Table 2.

ity become adjusted to the new conditions. In the tables these abnormally long cycles are indicated by parentheses ( ), and were not used in the calculations. In seven cases there was only a slight arrest of the rhythm or none at all. The average length for the first three cycles of the whole series was 8.9 days.

Following this postoperative lengthening the oestrual rhythm was reestablished, but the cycles became more irregular and somewhat longer on the average, as may be seen from Table 3. In all cases the dioestrum or rest period was the period which was lengthened, all of the other stages remaining well within the normal limits. In this series a total of 714 cycles was followed, giving a total average length of 6.0 days per cycle as against 4.8 days in the normal control series. This increase of 1.2 days or 25 per cent in the length of the cycle is quite consistent, and cannot be due to the prolonged cycles following the removal of the glands, since any of these exceeding nine days in length were not used in the calculations. As a further check the last fifteen cycles of each rat were considered, giving approximately the same average length.

In the eleven animals of the parathyroidectomized series a total of 258 cycles, exclusive of the lengthened ones following the operation, was followed, giving a total average length of 5.4 days or an increase of 12 per cent over the length of cycles in the normal controls. The same general considerations apply here as in the thyroparathyroidectomized series. The lengthening of the cycles again was consistent, the average of the last fifteen cycles of all rats giving approximately the same figure as the total average.

This lengthening of the oestrous cycles after thyroparathyroidectomy and parathyroidectomy is subject to the same possible explanations as is the lengthening after thyroidectomy. It is believed, however, that the evidence is stronger for the view that the effect is due to a disturbance of the general well-being of the animal and a lowering of the general bodily metabolism, rather than to the loss of any specific stimulatory effect of the thyroid on the ovary. The case of the parathyroidectomized animals strongly supports this view. It is rather difficult to imagine, and there is no evidence for, any direct causal relationship between parathyroid and ovary, yet there

was an average increase of 12 per cent in the length of the cycles after the removal of the parathyroids. In view of the rather serious effects of total thyroparathyroidectomy, or parathyroidectomy, such a disturbance might well be expected. These effects include the lowering of the general metabolic level; a decreased resistance to infection; disturbance of calcium metabolism, especially noticeable in the teeth; the lessened intake of food; and the resultant slowing of bodily growth, all of which are conditions that are usually reflected in prolonged oestrual cycles. That the lengthening may be entirely explained by these disturbed conditions is indicated by the 18 per cent increase in length of the cycles of the controls whose teeth were kept short in imitation of the condition in the parathyroidectomized animals.

It is worthy of note that in the thyroparathyroidectomized series, the effects of thyroidectomy and of parathyroidectomy here combined in the same animals, seem to be additive. These animals show an average length of cycle of 6.0 days, as compared with 5.8 days in the thyroidectomized and 5.4 days in the parathyroidectomized series. This additive effect is easy of explanation on the basis of a disturbance in general metabolism and well-being, but is difficult to explain otherwise. If it is due to a direct, specific effect, then the specific effects of the thyroids and of the parathyroids on the ovary must be the same, which is highly improbable.

SUMMARY

1. Using the length and character of the oestrous cycle as an index of ovarian activity, a study was made of the effects of thyroparathyroidectomy and parathyroidectomy in two groups of albino rats.

2. The cycles following total thyroparathyroidectomy showed an average lengthening of 1.2 days, or 25 per cent over those in normal control animals.

3. Following parathyroidectomy alone there was an average lengthening of the cycles of 0.6 days or 12 per cent over those in controls.

4. These results are considered as being due to the effects of the removal of the glands on general bodily health and

metabolism, rather than as a direct specific effect on ovarian activity. Trauma in sham operations and inanition due to clipping of incisor teeth gave similar results in control animals.

5. The effects of thyroidectomy and of parathyroidectomy on the oestrous cycles, seem to be additive when both operations are performed in the same animal.

It is a pleasure to acknowledge indebtedness to Professor R. G. Hoskins for generous advice and suggestions in regard to these studies.

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STUDIES ON VIGOR. VII. THE FATIGABILITY OF CASTRATED RATS

MARVIN GANS and R. G. HOSKINS

From the Laboratory of Physiology, Ohio State University

COLUMBUS

Studies on rats by the revolving cage method have shown that castration results in a marked decrease in voluntary activity. In one series of experiments (Hoskins, 1925) sixteen control and sixteen experimental animals were studied over a period of 120 days. From a group of about fifty young animals that had become accustomed to the apparatus sixteen pairs (mostly twins) were selected; these were well matched both as to weight and as to activity records over a preliminary period of 20 days. Then the more active of each pair was castrated, the age of the animal being about 70 days. Beginning at about the twelfth day, on the average, the activity of the castrated animals began to lag behind that of the controls. At the fiftieth day after operation, the activity of the control group was at its height, averaging approximately 15,000 yards a day, while that of the castrated group averaged about 3200 yards. At the end of 100 days the averages were about 6000 and 3100 yards, respectively. Numerous subsequent observations have confirmed these results. Directly or indirectly, therefore, the testes condition in an important way the spontaneous activity of the animals.

Available data offer little in the way of explanation of such findings. Some observers have reported a slight depression of basal metabolism, but others have failed to corroborate this (Lusk, 1925). Certainly the slight decreases of oxygen consumption noted by investigators who have obtained positive results could not explain a decrease in activity to only a fifth of the normal. Indeed, as Lusk suggests, the decrease of metabolism, if it occurs, is more likely the result than the cause of the sluggishness.

Several possible explanations suggest themselves. Perhaps the most plausible is that the general irritability of the nervous

system is depressed with resultant decrease in the number of "driving" impulses that reach the effectors. That the sensory organs themselves are depressed is not likely from what is known of their activity in eunuchs. In one human subject, well known to one of us, acuity seems to be unusually high. Numerous incidental observations of castrated rats in our colony also give the impression that there is no outstanding sensory factor involved. A study of central nervous irritability has been planned, but no instructive data have as yet been secured.

It was believed that the field could be narrowed somewhat by a quantitive study of the fatigability of nerve-muscle preparations, in situ. It was realized, however, that results of such a study would not be conclusive. If a depression were observed it might be due to lowered efficiency of the effectors or of the supportive functions, such as circulation, sugar mobilization or respiration. Conceivably peripheral degeneration of motor nerve fibres could also play a role.

METHODS

In the study herein reported male albino rats were used as subjects. The animals ranged in age from 170 to 337 days. In most instances litter controls were used. Most of these had been tested previously in revolving cages as earlier described. The animals were anesthetized with amytal*, which was injected subcutaneously so that uniform and prolonged anesthesia could be obtained. The sciatic was laid bare, sectioned near the hip joint and adjusted in a Sherrington electrode. The skin was then sutured over the incision. A medial incision was made into the thigh; by blunt dissection the femur was exposed and fixed by means of a small modified Harvard femur clamp. The gastrocnemius muscle was isolated from its distal attachment and connected by a strong linen thread to a heavy type Harvard muscle recording lever.

The approximate absolute strength of the muscle was first determined, using single break shocks of a maximal faradic current as stimuli. In order to obviate fatigue this orienting study was confined to four trials of each muscle. An initial weight of 250 grams was attached and the nerve stimulated. Using the first reaction as a guide, lead weights of the estimated required

*We are indebted to Eli Lilly & Co. of Indianapolis for a generous supply of amytal.

number were either added or removed, and the stimulus repeated. In practice it was found that the fourth trial was adequate to fix the limit rather accurately.

The muscle was then stimulated automatically at one second intervals by means of a faradic current, using make shocks only. The primary coil of a Harvard inductorium was connected with a battery of 6.2 volts, the current being made and broken by a chronograph every second, the contact being maintained throughout the interval. The secondary coil was fixed in the same position, 4 cm., throughout the series of experiments. The break stimuli were short circuited by means of a special device illustrated in Figure 1. From the binding posts of the secondary coil, two No. 28 cotton-covered magnet wires were led

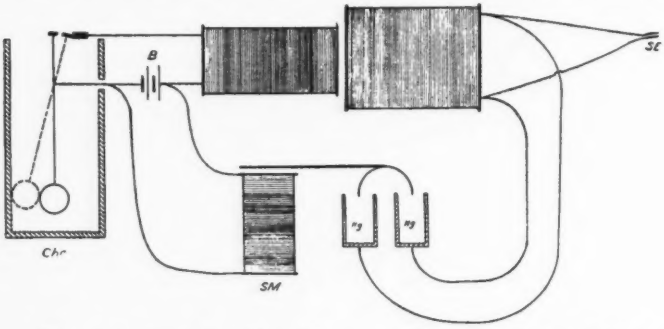

Figure 1. Short circuiting device. B., Battery connected with primary coil of Harvard inductorium. Chr., Automatic circuit breaker. S. M., Harvard signal magnet carrying curved metallic connector dipping into mercury cups, Hg. S. E., Stimulating electrode.

to the Sherrington electrodes, and two of No. 14 copper insulated wires were connected to two mercury cups. A signal magnet was connected with the battery. To the writing lever of the signal magnet an insulated U-shaped copper rider was attached. The signal magnet was so adjusted that when the current was made the rider was drawn down and into both mercury cups, and thus a short circuit was established. The lag of the signal magnet permitted the make current to reach the electrode and kept the circuit closed during the period of break. The chief practical difficulty encountered was in calibrating the diameter of the mercury cups to obtain the minimum surface tension effect. It was found necessary to connect

the primary of the inductorium and the signal magnet in parallel with the battery, and also to use a low resistance wire in the short circuiting device. By reversing the position of the signal magnet the make instead of the break shocks could have been eliminated.

The muscle was after-loaded with a weight of 50 grams and each contraction was registered by means of a slow-moving extension kymograph. The total amount of work was calculated by multiplying the summated height of the contractions by the weight lifted. No allowance was made for friction in the recording apparatus. At the conclusion of the experiment the muscle was dissected free and weighed.

OBSERVATIONS

In all, sixteen groups of two or three animals each were studied. These included 19 castrated and 18 control animals. Complete data as to work done were secured in 13 groups, comprising 15 experimental and 15 control animals. In 13 cases the total work done by the control animals was greater than that of the castrated, while in two instances the experimental animals surpassed the controls. The average amount of work of the controls in 12 groups in which complete data were secured was 107,924 gram-centimeters, while that of the castrates was 81,277 gram-centimeters. The ages at the time the final observations were made ranged from 170 to 331 days. The intervals between castration and ergograph tests varied between 95 and 277 days.

In view of the well marked difference in efficiency the question of weight and absolute strength of the muscles tested acquires a primary interest. In the 13 groups in which both total work and muscle weight were determined, this weight was greater in the castrated animals in all but two instances and the weights were equal in one of these. The averages in the 12 groups considered were respectively 2.10 and 1.86 grams. These differences were closely proportional to the total body weights which averaged 259 grams in the controls and 291 grams in the castrated animals. The ratios were 1:1.13 and 1:1.12, respectively; that is the muscle weight varied in the same proportion as the body weight.

The absolute strength of the muscle was greater in the con-

TABLE SHOWING RESULTS OF ERGOGRAPHIC EXPERIMENTS
Gastrocnemius muscle after-loaded with weight of 50 grams.

Animal No.	Age in Days	Interval After Castration	Weight of Animal	Weight of Muscle	Absolute Strength Grams	Absolute Strength per Gram	Total Contraction Cm.	Work Gm. Cm.	Work Kgm. Cm. per Gm.	Daily Activity
159E	326	246	281	2.29	320	140	2550.5	127525	55.69	821
161C	326		312	2.10	330	157	3027.7	151385	72.09	4538
162C	326		276	1.88	270	144	1312.2	65610	34.89	3025
148E	332	251	356	2.42	325	134	4732	236650	97.79	2341
151E	337	252	302	2.05	380	185	3820	191000	93.17	1761
152C	337		248	1.92	380	198	6004	300200	156.32	4483
215C	331		290	2.35	260	111	1245	62250	26.47	1625
216E	331	265	265	1.85	260	138	927	46380	25.03	866
218C	331		285	2.25	220	98	1383	69150	30.73	2041
278C	310		248	1.75	220	125	398	20900	11.94	2058
280E	310	229	276	2.25	210	93	793	39650	17.62	900
193C	315		325	2.20	250	114	2315	15750	51.61	2158
197E	315	267	345	2.37	250	106	722	36100	15.23	2791
174C	324		335	2.05	340	166	1721	86050	41.97	8341
175E	326	277	365	2.32	340	147	810	40500	17.45	2258
993E	174	94	310	2.55	290	114	1022	51100	20.04	2314
992C	174		212	1.47	290	197	2360	118000	80.27	6891
2082E	177	97	280	1.75	240	137	1071	53850	30.77	4236
2078C	179		160	1.08	210	194	1602	80100	74.17	18018
2080E	177	97	280	1.80	280	155	1434	71700	39.83	4653
*920C	207		310	....	310	....	1806	90300	.....	3300
*918E	207	184	320	2.80	270	....	962	48100	.....	1119
*917E	207	184	300	2.75	270	....	.....	.....	.....	751
989C	176		306	2.31	250	108	3826	191300	82.81	1856
988E	176	148	300	2.50	310	124	2940	122000	48.80	2340
1176E	170		....	2.05	310	151	792	39600	19.32	.....
1161C	170		....	1.80	280	155	1095	54750	30.42	.....
1177E	170		230	1.85	300	162	270	13500	7.29	.....
1162C	170		200	1.60	280	175	822	41100	25.69	.....
1178E	173		200	1.40	350	250	1368	68330	48.80	.....
1170C	175		180	1.40	300	214	3088	154400	110.30	.....
Averages Controls	260		259	1.86	279	153	21570	107924	59.26	5003
Experimentals	249		291	2.10	294	145	16608	81277	38.34	2298
974E	193	95	220	1.50	350	....	.....	.....	.....	5705
978C	194		180	1.30	320	....	.....	.....	.....	7100
971E	209	114	225	2.10	310	....	.....	.....	.....	607
969C	210		160	1.60	270	....	.....	.....	.....	1044
928E	281	185	....	2.25	270	....	340	17000	.....	686
929C	282		....	1.65	310	....	.....	.....	.....	1903

*Excluded from averages except absolute strength.
C—Control animals.
E—Experimental animals.

trols than in the experimental animals in 4 cases, less in 7 cases and equal in 5 cases. The averages in 12 groups were 279 grams in the controls and 294 grams in the castrates. When the absolute strength was calculated per gram of muscle, however, the results were as follows: controls greater in 10 and less in 4 cases. The averages in 12 groups were: controls 153, castrates 145, i. e., essentially equal.

The work done before complete fatigue was reached was greater in the control than in the experimental animals in 12

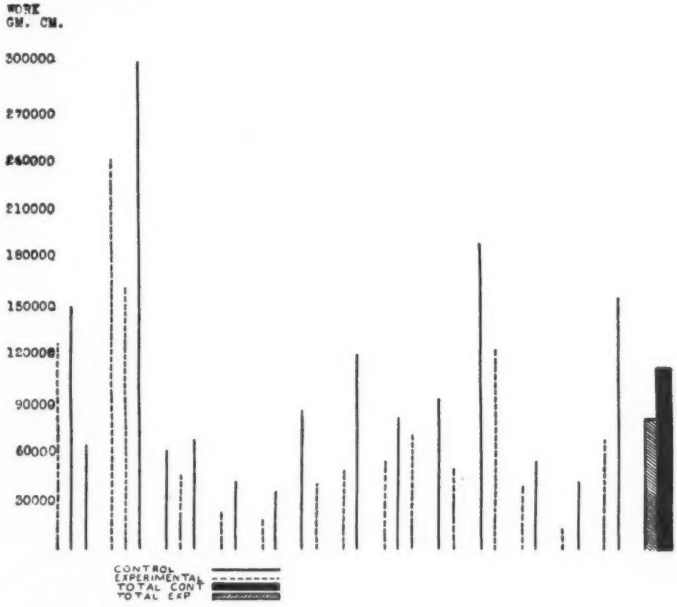

Figure 2. Work done by gastrocnemius muscles of castrated and normal rats. The muscles were stimulated through their motor nerves to the point of complete fatigue. They were after-loaded with 50 grams weight. In the graph for "total" read "average."

and less in 3 cases. The averages for 12 groups were: controls, 107,924 gram-centimeters; castrates, 81,277 gram-centimeters. Reduced to kilogram-centimeters of work per gram of muscle the results were: controls greater in 12 and less in 3 cases. The averages were: control, 59.26 kgm.cm. and experimental 38.34 kgm.cm. In Figure 2 the total work done is expressed graph-

ically. Even so considered, the advantage of the non-castrated animals is obvious. If the reduced data were plotted, the results would be even more striking.

In 10 of the 13 groups of animals activity cage records were available. These were averaged for the thirty days preceding the ergograph determinations. In all but two instances the controls were more active than the castrates. In most instances the differences were striking. The averages in 10 groups were: controls, 5003 revolutions; castrates, 2298 revolutions. Considering the fact that the controls in most cases were showing marked degrees of early senile depression, this difference is especially significant. If carried to extreme old age, no doubt the activity of both groups would become essentially equal and negligible. In a considerable number of senile animals that we have had under observation, the activity has amounted to less than 10 yards a day. Whether normal or castrated animals would attain this degree of sluggishness earlier is an interesting question that we have not studied.

DISCUSSION

Perhaps the most striking feature of the data at first glance is their marked lack of homogeneity. This might seem at once to indicate that they have little or no significance. Such a conclusion, however, is not justified. One of the surprising facts that has come out of the vigor studies we have made is that the spontaneous activity among litter mates varies widely. One animal is frequently several times as active as its twin, although both seem to be entirely healthy. For this reason the animals in such studies are always "typed" before any experimental procedures are begun. Hence, although there may be much variability as among groups, within the groups the initial activity is closely similar. In the experiments herein reported, the animals selected for castration were in general slightly more active than their controls. While there is considerable variability in this respect, in general the animals of a litter that are more vigorous in the earlier weeks continue to show this characteristic throughout the active period of their lives.

The experiments as a whole indicate that a considerable part of the sluggishness of castrated animals is to be ascribed to

lessened efficiency of the muscles. The only apparent escape from this conclusion would be to make the highly unlikely assumption that the motor nerves to the muscle are materially depressed in their irritability or, still less likely, in their conductivity. We know of no evidence that castration results in any such peripheral nerve changes.

Whether the decreased efficiency is due, however, to local changes in the muscle or to failure of supporting functions—circulatory, respiratory, or metabolic—the data give no evidence. The fact that the absolute strength of the muscles is not greatly different in the two groups suggests that the cause is to be sought elsewhere than in the tissues immediately involved. The investigation must obviously be extended to include a study of the effects of castration on the physiologic processes in general.

SUMMARY

1. A comparative study was made of the strength and fatigability of the gastrocnemius muscles of castrated and normal rats. The muscles were stimulated electrically through their motor nerves.

2. The weights of the individual muscles were greater in the castrated animals, but the absolute strength per gram of muscle averaged approximately the same in each group.

3. The proportion of gastrocnemius weight to total body weight averaged the same in each group.

4. The total work performed by the castrated animals was considerably less than that by the controls.

5. The increased fatigability of the castrated animals could be ascribed to lessened muscular efficiency, per se, but is more likely due to inadequacy of supporting functions, such as circulation or respiration.

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Book Reviews

INSULIN AND ITS USE IN DIABETES. J. J. R. Macleod and W. R. Campbell, 1925. The Williams & Wilkins Co., Baltimore.

The development of the insulin treatment of diabetes is an outstanding triumph of co-operation in research between the physiologist and the clinician. It is, therefore, altogether appropriate that volume six of Medicine Monographs, which deals with insulin and its use in the treatment of diabetes, should be the joint work of Prof. J. J. R. Macleod, physiologist, and Dr. W. R. Campbell, clinician, both of the University of Toronto. Dr. Macleod is responsible for the first sixty pages of the book. In the Introduction he briefly traces the history of the investigations which led up to the discovery of insulin by Banting and Best, and gives the results of a few of their experiments. This is followed by an account of the work of Collip in devising methods for the preparation and purification of insulin. An outline of the best methods in use at the present time for its quantity production is also given, and the nature of the numerous insulin-like substances that have been extracted from everything from yeast to clams is considered. Macleod discusses in a very illuminating way the results of the various experiments that have been performed on depancreatized dogs. He points out that insulin is necessary not only for the oxidation of glucose but also for the formation of glycogen, and suggests the possibility that the formation of glycogen may be a necessary step in the oxidation of carbohydrate. The fact that insulin reduces both the blood and the urine phosphates leads Macleod to the conclusion that glucose unites in some way with the inorganic phosphates of the blood. He points out that this view is supported by the findings of Embden and his collaborators, who have given evidence to show that a compound of phosphoric acid with a complex which yields lactic acid, undergoes decomposition during muscular work.

Several pages are devoted to a discussion of the present methods of both the physiological and clinical assay of insulin, and the shortcomings of these methods are clearly shown. The difficulty of establishing the glucose equivalent of a unit of insulin is also dwelt upon. The fact that in the early experiments depancreatized dogs treated with insulin invariably died, Macleod believes was due to the absorption of toxic substances produced by the action of intestinal bacteria upon imperfectly

digested proteins. This view is supported by the fact that in the later experiments in which the dogs were fed whole pancreas in order to supply them with trypsin, it was possible to keep them alive indefinitely.

The clinical section by Dr. Campbell includes a brief account of the early clinical experiments on insulin, an interesting discussion of the effects of insulin on metabolism, including the symptoms of hypoglycemia and the best method of avoiding this condition. This is followed by a thorough discussion of both the diagnosis and treatment of diabetes. Dr. Campbell feels that the patient should invariably be kept free from both glycosuria and hyperglycemia. This can be accomplished by the proper use of insulin and thus there is a possibility that the sugar tolerance of the patient may be increased. There is also a chapter on the dietetic treatment of the disease, which is supplemented by numerous recipes and tables of food equivalents. Full directions are given for making all the necessary blood and urine tests.

RATIONAL GLAND THERAPY FOR WOMEN PARTICULARLY IN RELATION TO MENSTRUATION. I. Wanless Dickson, 1926. H. K. Lewis & Co., Ltd., London. P. 96.

This small book is one of a type the popularity of which seems to be fortunately on the wane. It consists largely of a summary of well known gynecologic data interspersed with a considerable amount of dubious interglandular endocrinology. This latter is cited without convincing evidence and in disregard of conflicting results in the literature. True to type, in lieu of scientific evidence, the book contains illustrative superficial case histories.

Whatever value it may have is not in its "rationality" but as a record of the empirical experience of the author with gland therapy. His results have apparently been more satisfactory than those of most gynecologists.

THE PRINCIPLES AND PRACTICE OF ENDOCRINE MEDICINE. William Nathaniel Berkeley, 1926. Lea and Febiger, Phila. and New York. P. 368.

It is unusual that an author so accurately reviews his own book as has Berkeley in this case. In the preface he states: "The title of this book is meant to be accurately descriptive. The practice of endocrine medicine is becoming daily a more important and fruitful field of medical labor; that such practice may be intelligent and scientific, an acquaintance with the principles of the subject is indispensable. A sincere effort has been made to simplify these principles. In respect of points

in doubt a short summary of arguments pro and con is given; but as far as possible controversial matter is abridged or omitted, unsubstantiated claims are mentioned with proper reserve.

"The book is primarily meant for doctors in active practice. The standpoint of the writer is that of the clinical practitioner —the physician in the presence of a patient with endocrine disorder. Symptoms and diagnosis are discussed at length and treatment is emphasized. Many details of treatment and dosage are given which have been heretofore inaccessible in print in any language.

"It is hoped that for general readers also the book may serve a useful purpose. It defines the actual scientific status of endocrinology today, and contradicts at least a few of the old wives' fables now told not only in popular but in pseudo-scientific literature as well.

"In view of the practical aim of the book, many topics of exclusively scientific interest have been only touched on. But in each case, for the benefit of scientists and laboratory men, the important references to modern sources of information have been fully given, so that further special inquiry may be facilitated."

These aims have been admirably achieved. The text is entertaining and thoroughly readable. The illustrations are well selected and the book is well printed.

Perhaps the best test of a book of this sort is its treatment of "pluriglandular disorders"—a topic that exercises an irresistible appeal to romancing in the case of many writers. While Berkeley's chapter is brief, it is highly sensible and instructive. As to therapeusis he says: "An effort must be made in a rough clinical way (smaller children can rarely be kept quiet enough for a basal metabolism test) to estimate the amount of each deficiency, and the dosage should be adjusted and readjusted for each patient. I deprecate very much the slovenly habit of giving indiscriminately the ready-made 'shotgun preparations' of a half dozen different hormones for sale in the shops. The pharmacists could not sell these formulas if the physicians did not prescribe them."

To those whose needs can be met in a book of 350 pages this volume can be highly recommended.

Abstract Department

Suprarenal transplantation. Blodinger (J.), Klebanoff (H. E.) & Laurens (H.). Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23**, 22.

The left adrenal was removed from 15 dogs and a portion transplanted to some other site. Vascularization of the grafts was rapid. Living cells could not be demonstrated in them, however, after 34 days. When the intact right adrenal was removed all of the animals died, none surviving more than 4 days after the second operation, regardless of the age of the graft.—J. C. D.

Adrenal cortex and somatic growth (Corticale surrenale e accrescimento corporeo). Castaldi (L.), Arch. ital. di anat. e di embriol. (Firenze), 1925, **22**, 297-368.

The feeding of adrenal cortex of the ox to very young guinea-pigs favors the growth of the skeleton and the formation of muscle and fat. After development is complete feeding causes increase in weight of muscle and fat only. In respect to the action on the skeleton, the author believes it to be the direct action of certain unknown constituents of the adrenal cortex cells. Hence it is suggested that adrenal cortex be included with thyroid, hypophysis and thymus in treating conditions of undergrowth. The medullary substance should not be used, since it may prove harmful in long usage.—P. M. N.

The adrenals in pulmonary tuberculosis (Il sondaggio potenziale fisco dei surreni nella tubercolosi polmonare). Franco (P. M.), Folia med. (Napoli), 1925, **11**, 321-345.

The author by a method of applying Röntgen ray stimulation to the adrenals shows that with the progress of pulmonary tuberculosis the resistance of the glands becomes less and their activity is decreased.—P. M. N.

Investigation of the influence of the adrenals on the basic respiratory metabolism (Untersuchungen über den Einfluss der Nebenniere auf den respiratorischen Grundumsatz). Nakayama (K.), Biochem. Ztschr. (Berl.), 1925, **155**, 413-435.

A continuation of the author's preceding paper (Biochem. Ztschr., 1925, **155**, 387), using substantially the same experimental methods. The author finds that extirpation of adrenals from rats

lowers the basal metabolism but slightly if at all. Similarly, the results of feeding experiments with levulose and cane sugar do not differ materially in normal and adrenalectomized animals. Finally, the addition of thyroid in the feeding experiments induces no substantial change from those experiments in which it was omitted. (The accessory adrenal tissue of the rat robs these experiments of sharp definition.—Abstracter.) The protocols of the experiments are given in full.—A. W. R.

Suprarenal hemorrhage in the new-born. Joseph (S.) & Raban (E.), Zentralbl. f. Gynäk. (Leipz.), 1925, **49**, 1; Abst., Am. J. Dis. Child., **30**, 868-869.

Hemorrhages in the suprarenal glands as an accidental necropsy finding are frequently reported, but only a few cases have thus far been reported in which the hemorrhage was so extensive as to cause death. The authors report a case of a child born at term. The delivery was rather difficult, and the child was mildly asphyxiated but recovered without strenuous measures of resuscitation. Thirteen hours after delivery cyanosis appeared suddenly, and death occurred three hours later. At necropsy an extensive hemorrhage of the right suprarenal gland was found; there were no other findings, except a few small, superficial hemorrhages on the cerebral convexities. The authors conclude that venous congestion of the suprarenal, due to trauma during delivery, was followed thirteen hours later by hemorrhage, which finally ruptured the capsule and spread into the surrounding tissues.

Studies in adrenal insufficiency. Stewart (G. N.) & Rogoff (J. M.), Proc. Soc. Exper. Biol & Med. (N. Y.), 1925, **23**, 190-195.

It was found that pregnant and lactating bitches survived removal of both adrenals for a much longer period than nonpregnant bitches or males. Hemorrhagic congestion of the gastro-intestinal mucosa occurred commonly in dogs dying of adrenal insufficiency (47 out of 52). Congestion of the pancreas occurred in 50 out of 53 cases in operated animals and twice out of 20 cases in normal dogs. Blood or blood pigment was found in the intestinal contents at autopsy in 50 out of 54 adrenalectomized dogs. This is not derived from food. Blood examinations showed a reduction in the relative volume of the serum per 100 c.c. of blood and a reduced conductivity of the serum, a few days before death in the operated animals.—J. C. D.

Anatomy of the paraganglia in man (Zur Anatomie und Histologie der Nebenorgane der menschlichen sympathischen Nerven). Ivanoff (G.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1925, **75**, 435-443.

The paraganglia of 149 specimens (4 embryos, 122 children

from 1 month to 13 years, 20 adults from 18 to 70 years, 2 dogs and 1 cat were examined). The number, form, size and position of these masses in the region of the abdominal aorta were recorded. Persistent and nonpersistent paraganglia were recognized. The nonpersistent showed a slow growth from 12 months to 18 months, after which degeneration took place and the structure completely disappeared by the 10th to 13th year. These apparently carry on the adrenalogenic function up to the 12th to 18th months. After that time this function is carried on by the persistent chromaffin system. Vascular increase in the parenchyma, hyaline degeneration, decrease in the size and changes in the form, reaction and specific granulation of the chromaffin cells, growth of connective tissue and in lymphoid elements are all correlated more or less directly with age. Data are tabulated graphically.—A. T. R.

Endocrine glands in pernicious anemia. Mendershausen (A.), Klin. Wchnschr. (Berl.), 1925, **4**, 2089-2136; Abst., J. Am. M. Ass., **85**, 1924.

The author found the pituitary, pancreas, suprarenals and gonads practically normal in his thirteen cases of pernicious anemia. He found, however, in twelve of them changes in the thyroid gland (lymphocytic infiltrations with atrophy, occasionally increase in colloid).

Thyroparathyroid and gonadal effects on sedimentation of the red corpuscles (La reazione sedimentaria dei corpuscoli sanguigni suo comportamento negli stati tiroparatiroidei e genitalici). Vasaturo (A.), Folia med. (Napoli), 1925, **11**, 241-263.

The velocity of sedimentation of the red corpuscles is decreased in hypothyroidism and increased in spontaneous or experimental hyperthyroidism. Parathyroidectomy increases sedimentation velocity. The male gonads have no influence.—P. M. N.

Adiposis dolorosa (Dercum's diseases). Winkelman (N. W.) & Eckel (J. L.), J. Am. M. Ass. (Chicago), 1925, **85**, 1935-1939; Abst., A. M. A.

Winkelman and Eckel report one case and review briefly fifteen cases cited in the literature. The case described fits in with the generally recognized syndrome of Dercum's disease, showing the following features: (1) obesity (exclusive of face, hands and feet), weight 460 pounds (208 kg.), with painful masses; (2) ulcers on the legs and bullae on the fingers, and (3) asthenia. The pathologic findings were an adenoma of the anterior lobe of the pituitary body with enlargement of the sella turcica, an adematous hyperplasia of the left suprarenal, atrophy of the ovaries, and many recent hemorrhages in the thalamus and subthalamic regions. On

reviewing the necropsy findings of the fifteen cases in the literature, one is impressed by the pluriglandular involvement in most of the cases. In only two cases were there no definite changes in the ductless glands (Rome and Falta). Of the eleven patients in whom the pituitary body was examined, eight showed definite alterations; the thyroid was abnormal in twelve cases; the sex glands were pathologic in nine; the suprarenal in three, and the pancreas in two. The author's own case showed pituitary, suprarenal and ovarian pathologic changes. It is of interest from a clinical standpoint to note that the condition is five times more prevalent in the female and that most cases develop after the age of 35. The theory of endocrine malfunction seems best suited to explain the symptoms in this case.

A peculiar (hermaphroditic ?) ovarian tumour. Berner (O.), Arch. internat. méd. exper. (Liége), 1925, **1**, 825-848.

In a hen that had ceased laying and had developed masculine characteristics, autopsy showed a small tumor in the small ovary. Microscopically the tumor proved to be a sort of adenoma containing columns of large clear cells and cell masses. In some places there were found tubules resembling immature tubuli seminiferi containing two sorts of cells, some large and clear, resembling spermatogonia and some, dark and small. There were also found some large ovum-like cells surrounded by smaller, flat cells resembling follicular epithelium. The tumor had originated from the germinal epithelium of the ovary, prolifering into it and forming cords and cell masses resembling the egg-tubes of Pflüger. The author regards these structures as probably sex-cells resulting from parallel conjugation of the chromosomes, but conclusive evidence was not found. The literature on "folliculomata" is discussed. Earlier investigators agree that these ovum-like bodies are not at all ova, but the author states that in accordance with modern opinion and experience of the plasticity of the sex-cells egg-cells may really develop in an ovarian tumor.—Author's Abst.

Effect of injections of liquor folliculi (Effets de l'injection d'extrait de liquid folliculaire chez les femelles impuberes). Brouha (L.) & Simonnet (H.), Compt. rend. Soc. de biol. (Par.), 1925, **93**, 489-491; Abst., Physiol. Absts., **10**, 478.

The extract from liquor folliculi of the mare, obtained by successive treatment with alcohol, petroleum ether, and acetone, was dissolved in olive oil and injected into rats. Sexually immature animals were used and the changes produced in the vaginal secretion followed. Certain animals were killed at various stages and examined. Injection causes a cycle resembling normal oestrus. There are distinct hypertrophic changes in the uterus, but none in ovaries or mammary glands.

Effects of the injection of extracts of follicular fluid into sexually mature females. Brouha (L) & Simmonet (H.), Compt. rend. soc. de Biol. (Par.), 1925, **93**, 557-558,

Continued daily injections of follicular extract into normal females (rats) lengthen the period of oestrous but do not suppress the periodic appearance of leucocytes in the vaginal smear. Injections during the last two or three days of gestation have no effect upon the normal course of pregnancy. Injections during lactation induce oestrus without apparent modification of mammary secretion. More hormone than is needed to induce the reaction in the spayed adult is required for the normal immature female.—E. Allen.

The presence of the feminine sexual lipoid in bird eggs and in the ovaries of fish. Fellner (O. O.), Klin. Wchnschr. (Berl.), 1925, **4**, 1651-1652; Chem. Abst., **19**, 3496-3497.

Egg yolks and fish ovaries were subjected to a chemical process identical with that used for the preparation of the active mammalian ovarian lipoid. The product so obtained was then injected in the course of 8 days, into a 1 kg. rabbit, that had previously been deprived (operation) of 1 horn of its uterus. The animal was killed on the eighth day. The remaining horn of the uterus had enlarged to 11 times its original size under the influence of a lipoid extract from 30 eggs. An identical enlargement was obtained with the lipoid extract from 125 gr. of fish ovaries. The lipoid from 2 placentas produced a 16-fold enlargement in 8 days. The mammae were typically enlarged in every case. Histology is also given. The lipoid from 30 eggs is, therefore, equivalent in activity to more than 1 placenta or 90 corpora lutea. Some interesting deductions are made as follows: One egg contains as much active substance as 100 of the ordinary ovarian tablets and almost as much as 1 intravenous dose of ovarian lipoid. Eggs must have a tendency to augment the bleeding of puberty and menstruation and should be avoided at this time. The amenorrhea of war may have been partially due to a lack of eggs in the diet. Since ovarian extract produces a hypertrophy of the mammae but inhibits milk secretion, eggs should be advantageous during pregnancy and contraindicated during lactation. It is also interesting in this connection that both eggs and caviar have long been classed as aphrodisiacs by the general public.

The female sex hormone. Frank (R. T.), Kingery (H. M.) & Gustavson (R. G.), J. Am. M. Ass. (Chicago), 1925, **85**, 1558-1559; Abst., A. M. A.

Experiments reported by Frank, Kingery and Gustavson not only indicate that puberty can be accelerated artificially by injection of the female sex hormone, but also that as soon as the thresh-

old is once passed, the ovaries, which appear to respond more slowly than the tubular system to the female sex hormone (after a short latent period), can function just as in the adult. No evidence of stimulation of ovogenesis and the new formation of ova could be obtained even after continued injection of the hormone (up to twelve days). Injection of the female sex hormone into immature female white rats in from three to five days causes opening of the canal and estrual phenomena (pubertas praecox), without the occurrence of ovulation. After a further interval of from five to seven days, the artificially produced puberty may be followed by spontaneous regular cyclical phenomena consequent to follicle ripening and ovulation. If the threshold of puberty is once crossed, sexual maturity may be maintained spontaneously in immature rats. These findings are said to indicate that puberty results from the elaboration, in sufficient amount, of the female sex hormone, and that the advent of puberty is not due to the removal of an inhibitory influence, such as might be exerted by one or more of the glands of internal secretion, such as the thymus or the pineal.

Influence of the ligation of the seminal ducts on the internal secretion of the testicles. Futakawa (M.), J. Okayama Med. Soc., 1925, 423, (April); Abst. Japan Med. World, **5**, 300.

Experiments were made on albino rats. It was observed that ligating the seminal ducts of old animals led to earlier degeneration of testicles and earlier death than in control rats. In the experimental rats there developed an abnormally accelerated desire for sexual intercourse, which was remarkable, but passed away very soon.—R. G. H.

Tumors and sex characteristics (Tumoren und Geschlechtscharaktere). Halban (J.), Ztschr. f. Konstit. (Berl.), 1925, **11**, 294-326.

After a consideration of numerous cases, mostly from the literature, it is concluded that neoplasms of the **adrenals and sex glands** may influence morphologically the sex characteristics. The influence of the **pineal gland** on sexual precocity is still uncertain.
—A. T. R.

A case of retarded growth (Ein Fall von Kleinwuchs mit kongenitalen Bildungshemmungen). Hammerschlag (E.), Ztschr. f. Konstit. (Berl.), 1925, **11**, 744-753.

The physical status of a 16-year-old girl is given and the cause of retardation and endocrine involvement discussed. In addition to over weight and under height, there were bilateral congenital shortness of fourth and fifth fingers and third and fourth toes. After **thyroid** tablet feeding for four months, plumpness decreased and the child did better in school. The **sex organs** were infantile.—A. T. R.

Hormone of the ovarian cycle. Hart (C. P.), de Jongh, Laquer & Wijsenbeek, Deutsche med. Wchnschr. (Berl.), 1925, **51**, 1700; Abst., J. Am. M. Ass., **85**, 1679.

The authors confirm fully Allen and Doisy's results with the follicular fluid. Besides this, they were able to obtain a protein-free solution with the same effects on the castrated mice.

Disproportion of the extremities in a eunuchoid giant (Die Disproportion der Extremitäten bei eunuchoidem Hochwuchs). Henckel (K. O.), Ztschr. f. Konstit. (Berl.), 1925, **10**, 577-580.

Physical measurements are given of a 23-year-old man 187.7 cm. long showing unusually long legs (105.9 cm.) and arms (85.6 cm.).—A. T. R.

The influence of the ovary on the absorption of the pubic bones of the pocket gopher, Geomys busarius (Shaw). Hisaw (F. L.), J. Exper. Zool. (Balt.), 1925, **42**, 411-441.

The pubic bones of both males and females of this species are the same up to the time of sexual maturity. In the mature animal the male symphysis pubis is well developed, while in the female the two pubic bones are normally widely separated. The resorption of the pubic bones in females is accomplished by osteoclastic activity. Castrated control males did not lose their symphyses. Injection of ovarian extracts into both castrated and normal males caused the dissolution of the symphyses. Spayed females, however, may also lose their pubic symphyses. Grafts of testicular tissue into young spayed females prevent resorption of the pubic bones. The femurs are not affected by injections which apparently influence only the pubes.—E. Allen.

The influence of the male sex gland on the female. An experimental study to determine the sex ratio of the offspring. Kovacs (F.), Am. J. Obst. & Gyn. (St. Louis), 1925, **10**, 527-544.

Attempts were made to influence the sex ratio of the offspring by the subcutaneous injection of fresh testicular substance into female albino rats. Each of six rats received in six injections a total equivalent of three-fourths of a testicle from young males. Matings were made at the beginning of the injections. A total of 49 offspring were produced, the ratio of males to females being 133:100 as against a normal ratio of 105.5:100. Five other animals received injections of testis tissue beginning eight days before, and continuing several days after, mating. A temporary sterility of from 3 to 11 weeks was produced. In 27 offspring from this series the ratio of males to females was 145:100. Of six females in which testes from young males were successfully transplanted

intraperitoneally, four animals gave birth to 21 young, the sex ratio of males to females being 250:100. The explanation is offered that in these cases there is a high mortality of female-producing ova and embryos. This is also indicated by the small number of young per litter, 5.2 as against 7 or 8 in the normal. As the writer states, the paucity of experimental animals in the series precludes "drawing far-reaching conclusions."—M. O. Lee.

Effect of prepuberty castration on subsequent cancer inoculation. Murphy (J. B.), & Sturm (E.), J. Exper. M. (Balt.), 1925, **42**, 155-161.

Male and female mice castrated during the first seven weeks of life and implanted with cancer at later periods of life show a resistance definitely higher than do intact animals of the same age. This increased refractiveness is evident at three months after the operation, but is more pronounced at eight months to a year. Even castration in early adult life seems to increase the refractory state to later cancer inoculation. On the other hand, adult mice inoculated within a week after castration show slight if any evidence of increased resistance.—Author's Abst.

Testis and hypophysis (Keimdrüse und Hypophyse). Nukariya (S.), Klin. Wchnschr. (Wien.), 1925, **4**, 1307-1308; Abst., Physiol. Absts., **10**, 422.

Histological observations on the effect of castration of male rats at various ages on the pituitary. A new type of cell is produced (illustrated), containing a large vacuole filled with colloid material. It has a diameter of 20 to 25 microns. These new cells are present a few weeks after castration, even in animals castrated when 1 to 2 months old. The changes in the pituitary are therefore not dependent on the maturity of the testis.

Influence of partial extirpation of the thyroid and adrenals in the parents on the endocrine system of their offspring (Ueber den Einfluss experimenteller Schädigung von Schilddrüse und Nebenniere der Eltern auf das endokrine System der Nachkommenschaft). Seitz (A.) & Leidenius (L.), Ztschr. f. Konstit. (Berl.), 1925, **10**, 539-566.

These experiments were made on rabbits. The most constant results were an increase in the hypophysis to two and three times the normal size in the first litter following thyroidectomy in the parents and distinct enlargement of the thymus of the young after adrenalectomy in the parents.—A. T. R.

On the influence of the placental extracts upon the female genital organs and other viscera. Suzuki (S.), Journal Chiba Med Society, 1925, **3** (January); Abst., Japan Med. World, **5**, 359.

The author observed that by the administration of placental extracts the thymus underwent atrophy, while the thyroid was hypertrophied. The uterus was hypertrophied, while the ovary had the follicles fully developed.

The behavior of embryonic chick gonads when transplanted to embryonic chick hosts. Willier (B. H.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23**, 26-30.

One group of chick gonads was transplanted at a stage before their sex could be determined (4 to 6¾ days of incubation). Another group was transferred after differentiation had taken place (7 to 13 days). The chicks were incubated 9 days and then examined. The grafts grew into right or left gonads according to the side from which they had been taken and into testes or ovaries according to their own potentialities regardless of the sex of host. The gonads of the host produced no abnormal changes nor variations in the development of grafts of the opposite sex. No evidence could be found of the grafted glands influencing the growth of the gonads of the host.—J. C. D.

The action of x-rays against the testicles of the albino rat, together with the vital staining of the interstitial cells. Yamakawa (H.), J. Toyko Med. Soc., 1925, **39** (May); Abst., Japan Med. World, **5**, 297.

The author exposed the testicles of albino rats to various lengths of x-rays, ranging between 0.08-0.18 AE, and found that all sorts of the rays produced almost the same destructive action against the interstitial cells. If the equal amount of different qualities of the rays should be absorbed, the results would be the same pathological changes. The spermatozoa are destroyed first, the spermatids next, while the spermatocytes are most resistant of all. One skin unit of x-rays would completely destroy the testicular cells. Sertoli's cells have higher resistance than the other cells, even than the interstitial cells. The changes in the testicular tissues do not develop evenly, but locally. The changes involve both the nucleus and the protoplasm. Altmann's granules disappeared sooner than did the nucleus. By x-rays the destruction of sperm cells is more complete than by mechanical means, such as ligation of the seminal ducts, atrophies caused by diseases, transplantations, etc. The normal interstitial cells atrophied and disappeared completely after the exposure. They are hardly stainable by the vital staining method, but when they are atrophied they easily take vital staining, and present histiocytal changes.—R. G. H.

The sella turcica. Camp (J. D.), J. Am. M. Ass., (Balt.), 1926, **86**, 164-167.

Observations based on anatomic specimens and roentgeno-

grams show the normal sella to vary in contour and size. Variations in contour may be classed into three types: the round, oval and flat, of which the oval type predominates in the adult. The average sella will measure 1.06 cm. and 0.81 cm. in the anteroposterior and vertical directions, respectively. Variations in the shape of the clinoid processes are numerous, and union between the anterior, middle and posterior clinoids, producing a bridged sella, occurs in about 5% of cases. Such an anatomic variation seems to be of no clinical significance. Pseudo-defects and apparent anomalies of structure are easily produced in a roentgenogram by faulty localizing technic. Pathologic conditions producing changes in the cell are numerous, and the differentiation of these changes as to cause is difficult. Owing to the characteristic deformity of the sella usually produced by each, the differentiation between an intrasellar and an extrasellar lesion is generally possible.—Author's Summary.

Action of placental, ovarian, and luteinic extracts on female generative organs (Ricerche comparative intorno all' azione di estratti placentari, ovarici e corpoluteinici sull' apparato sessuale femminile). Ceresoli (A.), Atti d. Soc. lomb. di sc. med. e biol. (Milano), 1924, **13**, 290-296; Abst., Physiol Abst., **10**, 538.

Alcohol-ether, acetone, and other extracts of either the ovary or the corpus luteum have an action similar to that of placental extracts on the generative organs of young rabbits and guinea-pigs. The stimulating action of placental extracts, particularly on the muscular coats of the uterus, is considerably greater than that due to either ovarian or luteinic extracts.

Pregnancy blindness and acromegalia (Schwangerschaftserblindung und Akromegalie). Frankl (O.), Ztschr. f. Konstit. (Berl.), 1925, **11**, 166-169.

The author describes a woman who became totally blind in the last months of pregnancy. A few weeks post-partum the features became acromegalic, although vision returned, indicating that although the hypophysis became smaller there persisted a physiological alternation in this organ sufficient to bring about the symptoms of acromegaly.—A. T. R.

The activity of human pituitary extracts (Ueber die Wirksamkeit der Hinterlappensubstanz der menschlichen Hypophyse). Lampe (W.), Wien. klin. Wchnschr. (Wien.), 1926, **39**, 15-16.

Assays were made of extracts of hypophyses from 20 human subjects. It was found that the posterior lobes gave potent desiccated preparations as determined by experiments on urine secretion, blood pressure and uterine contractions. The content of active sub-

stance from one gland to another showed considerable variation. The extracts were found to be notably stable.—R. G. H.

Action of pituitary extract on the uterus. Rucker (M. P.), J. Am. M. Ass. (Chicago), 1925, **85**, 1637-1639; Abst., A. M. A.

The author shows that the action of pituitary extract on the uterus is quite characteristic. It never gives contractions with periods of rest between, but always a continuous series of contractions with increase in intra-uterine pressure. This action was illustrated in a case of inevitable abortion in which the labor was induced in the fourth month with a number 3 Voorhees bag. The patient was given ¼ grain (0.0162 gm.) of morphine and 1/150 grain of atrophin at 1:30 p. m. At 8 p. m. she was having painless contractions of the uterus that averaged 10 mm. Hg, at intervals of two minutes. She was given 5 minims (0.3 c.c.) of pituitary extract subcutaneously. Five minutes later there was a characteristic pituitary extract action. The contractions increased in height only very slightly, but were continuous one after another, without any period of rest. Twenty-two minutes elapsed before there was the slightest pause between contractions. The intra-uterine pressure was increased 6 mm. of Hg. The patient still felt no pain. In other words, here was a dose so small (considering the stage of pregnancy) that it caused no action clinically, and yet produced an incomplete tetanus of the uterus.

Roentgen-ray treatment of pituitary tumor. Towne (E. B.), Arch. Neurol & Psychiatry (Chicago), 1926, **15**, 92-102.

Two cases are reported in which the visual fields and visual acuity returned to normal following cross-fire treatment with one-third of a maximum skin dose of roentgen-ray once a month. No recurrence has taken place up to the present time, three and one-fourth and two years after the treatments were started. In the first case, a partial external ophthalmoplegia disappeared promptly, and measurable decrease in the size of the large intracranial extension of the tumor was demonstrated by shifting of areas of calcification in roentgenograms taken before, and two and a half years after the institution of treatment. All adenomas of the pituitary gland should be followed by repeated perimetric examinations. Operation should be undertaken only if visual acuity and the fields do not improve. There is good reason to believe that when roentgen-ray treatment gives a favorable result the risk is less and the result more lasting than that of surgical treatment.

—Author's Summary.

The action of insulin in the spasmophilia of infants. Adam (A.), Klin. Wchnschr. (Wien.), 1925, **4**, 1551-1552; Abst., Chem. Absts., 1925, **19**, 3307.

Rickets and spasmophilia are due to a disturbance in carbohydrate metabolism. Assimilation metabolism, which is necessarily great in growing animals, is dependent upon maintenance metabolism, which is essentially a carbohydrate and fat combustion. Anything that reduces the latter will injure the former (vitamin deficiency, fever, infectious diseases, lack of nourishment) and tend to produce spasmophilia. Conversely, easily assimilable food (cod-liver oil) or irradiation with ultra-violet light tends to reduce spasmophilia because they enhance maintenance metabolism. Carbohydrate metabolism can be enhanced by increasing the concentration of glucose in the blood (diet rich in sugar, and demobilization of glycogen by injecting adrenaline or acid) and by facilitating its fixation to the body cells (insulin). Spasmophilics who have been treated with sugar, insulin and adrenaline show either a reduction or a complete cessation of symptoms. Details of treatment are given.

The reduced sensitivity to insulin of rats and mice fed on a carbohydrate-free excess-fat diet. Bainbridge (H. W.), J. Physiol. (London), 1925, **40**, 293-300.

Bainbridge used young rats divided into two groups, body weights and sex not given, as he found these not to be factors. To one group was given free access to the Halliburton-Drummond complete diet, to the other a similar diet except that the starch was replaced by butter of equal caloric value. Blood sugar tests and objective symptoms showed that the rats on the excess-fat diet developed a high resistance to insulin, much higher than the control group or that shown by rats upon ordinary laboratory diet. It is suggested that the explanation may possibly be hyperfunction of the thyroid on the excess-fat diet since it had previously been shown that excess-fat diet causes hyperplasia of the thyroid and that thyroidectomized rabbits are unusually sensitive to insulin. However, Bainbridge could not find, by weights or histological examination, any conclusive evidence of hyperplasia in the thyroids of the rats fed on the excess-fat diet. Bainbridge also found some evidence, but not conclusive, that excess-carbohydrate fat-free diet rendered rats more sensitive to insulin.—R. J. Seymour.

A case of infantile diabetes treated with insulin. Bowcock (H. M.) & Wood (J. A.), J. Am. M. Ass. (Chicago), 1926, **86**, 104-105; Abst., A. M. A.

Bowcock and Wood report their experience with eighteen months' treatment of an infant in whom diabetes was discovered at 16 months of age. Diet regulation and administration of insulin constituted the treatment. The striking feature in this case has been the practically normal increase in height, in contrast to the stunting of growth that was observed in diabetic children before the

advent of insulin. This case has been successfully managed without blood sugar determination, but the authors do not recommend the disregard of this helpful adjunct to the control of treatment. Blood sugar readings have seemed valueless in this case because of the apparent lability of the metabolic processes in this child. There was frequently observed in from two to three hours' time a change from a urine that was free of sugar and diacetic acid to a specimen loaded with both. Insulin reactions could be recognized only by objective symptoms, since the patient was unable to communicate his subjective feelings. Because of the difficulty in recognizing hypoglycemic reactions before they were well developed and because of the apparently very rapid change in blood sugar levels, the attempt to keep the urine constantly sugar free was abandoned. As the patient has grown older, this apparent lability of metabolism has decreased somewhat, and consequently it has been possible to decrease the insulin dosage slightly and give it in two daily injections instead of three. The decrease in insulin dosage while taking a quite constant and uniform diet suggests some improvement in tolerance.

Treatment of diabetes by raw fresh gland (pancreas). Carrasco-Formiguera (R.), Brit. M. J. (Lond.), 1925, **3378**, 552-554.

The claim has recently been put forward that the ingestion of raw pancreas is highly beneficial in diabetes. This claim was tested by Carrasco-Formiguera on a boy of 7 who had not received insulin. The results were convincingly negative. The first day of subsequent insulin treatment diminished the urinary sugar to a trace. —R. G. H.

The influence of the vagus on the islets of Langerhans. Part I. Vagus hypoglycemia. Clark (G. A.), J. Physiol. (Lond.), 1924-1925, **59**, 466.

It has been shown that the secretion of insulin is not necessarily dependent on the nerve supply to the islets; yet it is not unreasonable to suppose that the nervous system may influence their secretion, especially as there seems to be an antagonism between the sympathetic and parasympathetic systems. Possibly some mechanism of the parasympathetic system counteracts the hyperglycemia of sympathetic activity. Ergotamine does not cause a lowering of blood sugar, but when followed one hour later by pilocarpine or by guanidine, hypoglycemia results. That this is evidence of vagus influence is shown by the fact that after secretion of the vagus no hypoglycemia results from the injection of ergotamine followed by guanidine. It is concluded that stimulation of the vagus causes a secretion of insulin, which in turn causes hypoglycemia.—T. C. B.

An unusual case of hyperglycaemia (1.7%) with coma; associated with absence of acetone in the urine. Argy (W. P.), Boston M. & S. J., 1925, **193**, 1236-1237.

A case is reported of coma in a colored male, aged 33, with typical symptoms of diabetes mellitus, existing over a period of six months and ending in death. It is marked by an absence of ketonuria, a high blood sugar concentration and a large amount of acetone in the spinal fluid. Nephritis was observed and this is suggested as a factor in the failure to excrete acetone. Active treatment with insulin, begun some hours after the onset of coma, reduced the blood sugar from 1714 mgm. per 100 cc. to 895 mgm. The patient, however, remained in a comatose state until death.

—J. C. D.

Effect of insulin injection on the composition of milk. Kamitani (E.), J. Pediat. (Tokyo), 1925, 921; Abst., Am. J. Dis. Child., **30**, 719.

Kamitani experimented with two goats soon after they gave birth to kids. Insulin, distributed by the Cannaught Laboratories, was injected to the amount of 1 to 3 units per 2,000 kilograms of body weight and the milk was expressed at two hour intervals. The experiment demonstrated that the lactose in the milk showed a decrease of 17 per cent., and the duration of low carbohydrate was prolonged by increasing the dose of insulin. The acidity of the milk was also decreased at the same rate as lactose. The fat greatly increases in amount if the milk is expressed frequently, and the viscosity also increases proportionally. Giusti and Rietti once concluded that the milk fat is increased by insulin, but our experiment shows that the increase is not due to insulin. The effect of insulin on total nitrogen, calcium content, water and specific gravity is uncertain.

Glucose infusions and insulin in the preparation of poor surgical risks. Fisher (D.) & Mensing (E. H.), Boston M. & S. J., 1925, **193**, 712-714.

The glucose is given intravenously very slowly. The injection should take not less than 90 minutes. One unit of U20 insulin is given for every 2 grams of glucose. Half of this amount is injected subcutaneously, when one-third of the glucose has been given, and the other half of the insulin when the glucose injection is completed. By following the urine and, if possible, the blood sugar closely accidents have been avoided. The authors found this method successful in 18 cases of shock and others have used it in acidosis of non-diabetic origin. The authors conclude that glucose infusions and insulin administered before operation in acute surgical conditions complicated by acidosis, shock, or incessant vomiting,

greatly diminish the operative risk and mortality, and transform a poor surgical risk into a fair or good risk. In general routine cases, particularly in gastric and gastro-intestinal conditions with or without inanition, glucose infusions and insulin have a remarkably invigorating effect, and greatly increase the operative percentage of safety. Glucose and insulin are indicated in those cases in which the patients are in good preoperative condition, but who are to undergo a serious operation, in which some difficulty is anticipated.—J. C. D.

Trypsin and insulin injections into the pancreatico-duodenal artery. Friedmann (T. E.) & Webb (P. K.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23**, 69-72.

The observation concerning insulin is that when injected by this route in dogs it produces the characteristic fall in blood sugar. This is the opposite of what was found in cats by Epstein.—J. C. D.

Significance of change in oxygen absorption after insulin in normal rabbits. Hawley (Estelle E.) & Murlin (J. R.), J. Exper. Biol. & Med. (N. Y.), 1925, **23**, 130-131.

The oxygen absorption as determined in respiration experiments rises the first hour after insulin injection and falls considerably below the pre-insulin level the second hour. The CO_2 elimination rises the first hour. The second hour it rises only slightly if at all and returns toward the pre-insulin level in the third and fourth hours. Study of the urinary nitrogen indicates an abrupt change in metabolism from fat to carbohydrate about 1¾ hours after insulin. The diminished oxygen absorption for the second period is regarded as not due to the depression, but to the fact that additional oxygen is made available for combustion by bringing carbohydrate into metabolism in place of fat.—J. C. D.

Spontaneous disappearance of diabetes. John (H. J.), J. Am. M. Ass. (Chicago), 1925, **85**, 1629-1631; Abst., A. M. A.

Two cases of diabetes associated with acromegaly with the data on a few other cases that have recently appeared in the literature have given the author a basis for serious consideration of the possibility of effecting a cure in certain cases of diabetes. In the two cases reported, a cure appears to have been established, as is indicated by the normal glucose tolerance curve secured in the first case, and in the presence of normal blood sugar values on a very heavy diet in the second. These cases add further evidence to the cases of apparent cure previously reported in the literature, and to the experimental work of Copp and Barclay in support of the belief that up to a certain stage the diabetic process is reversible.

The reduction of the death rate from diabetes, particularly from diabetic coma in Massachusetts. Joslin (E. P.), Boston M. & S. J., 1925, **193**, 707-712.

The author first considers the statistics of deaths from diabetes and then gives brief instructions for the use of modern methods in treating diabetic coma. Deaths from diabetes per thousand of population have been on the increase since 1880. The rate of increase, however, has been getting less. The actual deaths in 1924 were fewer than for 9 years previous, omitting the war years, 1918-1919. The death rate from diabetes in Massachusetts per thousand is nearly twice that of London. In the first 3 decades the death rates are similar. In the fourth and fifth decades there are nearly twice as many deaths in London as in Massachusetts. This relation is reversed in the sixth decade when the diabetic deaths are higher in Massachusetts.—J. C. D.

Lactic acid and inorganic phosphorus of normals and diabetics after glucose, with and without insulin. Katayama (I.) & Killian (J. A.), Proc. Soc. Exper. Biol & Med. (N. Y.), 1925, **23**, 173-176.

In rabbits under urethane there was little change in the blood lactic acid after insulin. In normal human subjects at rest the lactic acid in the blood rose after the ingestion of 50 grams of glucose by mouth to 2 or 3 times its normal level. When insulin was given 2 to 3 hours following the glucose meal the lactic acid rose from 4 to 10 times its normal level. The lactic acid rose as the sugar fell. In diabetics glucose produced an increase of 50 to 100 times the normal amount of lactic acid. Insulin produced a rise, but not as marked as that in the normal subject. Insulin reduced the organic phosphorus in the blood and urine of both normal and diabetic subjects.—J. C. D.

The effect of insulin upon the metabolism of certain bacteria. Kendall (A. I.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23**, 62-64.

Bacteria were grown in plain glucose broth and glucose broth containing insulin. The ability of the bacteria to utilize the glucose was then measured by the changes in the titratable acidity and hydrogen ion concentration. In the first group bacteria not normally utilizing glucose were tested; among them Bacillus alcaligenes and Micrococcus catarrhalis. The second group comprised Bacillus bulgaricus and Bacillus acidophilus, which, it has been reported, use more glucose in the presence of insulin. The third group was chosen from widely different groups and included several types of pneumococci, streptococcus hemolyticus, and staphylococcus aureus. In no case did insulin have any demonstrable influence on the organism's ability to use glucose.—J. C. D.

On the mechanisms of recovery of glycemia after the action of insulin (Sur les mecanismes de recuperation de la glycemie apres l'action de l'insuline). Lewis (J. T.) & Magenta (M.), Compt. rend, soc. de Biol. (Par.), 1925, **92**, 821-822.

The mechanisms which cause recovery from the transient hypoglycemia caused by insulin are probably the same as those which cause hyperglycemia. Section of the splanchnics augments the sensitiveness to insulin. Hypoglycemia and convulsions follow a dose which only produces a moderate degree of hypoglycemia without convulsions in the controls. Section of the nerves of the hepatic pedicle augments slightly the sensitivity to insulin. Section of the two vagi diminishes the sensitivity a little. Simultaneous section of the splanchnics and vagi causes a disappearance of the marked sensitivity to insulin, but it is still somewhat greater than usual. Extirpation of the suprarenals in two operations, increase markedly the sensitivity to insulin. Suppression of the secretion of adrenalin either by extirpation of the medulla, or by removal of one suprarenal and denervation of the other, augments the sensitivity, but not as much as section of the splanchnics.—T. C. B.

Attempt at a surgical treatment of diabetes. Mansfield (G.), Klin. Wchnschr., 1924, **3**, 2378-2380; Abst., Chem. Absts., **19**, 3306.

The original idea was to sever the pancreatic duct, thus blocking the external secretion of the pancreas which might intensify the internal secretion. This was not tried because of the probable deleterious effect on food digestion of eliminating the pancreatic enzyme. A ligature was passed beneath the pancreatic vein and artery in the head of the pancreas and the pancreas tied off, exclusive of the blood supply, at this point. In this way only a portion of the external secretion of the pancreas was blocked. Dogs that had been so treated were persistently hypoglycemic after the effects of the surgical shock had subsided; they also showed an enormously high sugar tolerance which indicates that the internal secretion of the pancreas is increased when the external secretion is blocked.

Analogous action of insulin and epinephrin on the liver. Müller (E. F.) & Petersen (W. F.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23**, 47-51.

The administration of .05 mg. of epinephrin per kilo of body weight raises the blood sugar of an animal (dog?) 50 per cent in two hours. Administration of 0.5 units of insulin similarly lowers it the same amount. If these doses are injected subcutaneously at the same time either separately or mixed, there is a decrease in blood sugar. In more than 60% of the cases this is greater than insulin alone would give. If the epinephrin is given 20 minutes before the insulin, the results are similar. These observations do not agree with those of MacLeod. He found that if the proper

amount of epinephrin was injected one hour after an insulin injection, there would be a counter balancing action between the two with a stabilizing of the blood sugar level. MacLeod considered that his experiments showed an antagonistic action between insulin and epinephrin. The authors take a different view. Insulin has two actions. The first is through the nervous system from the tissue depot where it is injected and results in the synthesis of glycogen by the liver. The second is the hormone action on the tissues resulting in their increased utilization of glycogen with the corresponding decrease in the amount in the blood. The authors explain the apparent conflict between their results and those of MacLeod as follows: Epinephrin given before or simultaneously with insulin delays the absorption of insulin; the nerve effect of the insulin depot initiates glycogenesis in the liver, and decrease in blood sugar follows. Epinephrin given an hour after insulin injection (when insulin has been completely absorbed and has reached its maximum effectiveness) mobilizes glucose from the liver, and thereby increases the already existing glucose mobilization. The glycogen store of the liver may thereby be practically exhausted, but the blood sugar level is maintained by the sufficiently rapid mobilization of glucose from the liver.—J. C. D.

The use of high carbohydrate diets in the treatment of diabetes mellitus. Sansum (W. D.), Blatherwick (N. R.) & Bowden (Ruth), J. Am. M. Ass. (Balt.), 1926, **86**, 178-181.

With the use of high carbohydrate diets (2 or more gm. carbohydrate per gm. fat) it has been found possible to keep patients sugar-free and with a normal blood sugar. The patients are restored to a more nearly normal state of physical and mental activity. They are freed from the slightest traces of the acetone type of acidosis. The use of potatoes, milk and fruits has permitted the elimination of the acid-ash type of acidosis, which is believed to have been a cause of the high incidence of blood vessel disease. The diets are palatable. The patients lose their craving for forbidden foods, especially for the carbohydrates. A somewhat lower caloric intake is apparently required for full maintenance. These diets are cheaper, because they contain no special foods and much less of the expensive fats, such as cream, butter and olive oil. Theoretically, at least, and because of the entire freedom from acidosis, such diets should afford the patients the best opportunity for partial recovery.—R. G. H.

A study of the mechanism of insulin. Part I. The action of insulin and of the salts of guanidine on the permeability of the mammalian erythrocyte. Secker (J.), J. Physiol. (London), 1925, **40**, 287-292.

From the brief review of the literature given, Secker feels

justified in concluding that whatever the fate of glucose under insulin that immediate and complete oxidation in the tissues does not occur. The suggestion of Haldane, Kay and Smith that insulin may cause changes in the permeability of the body cells led Secker to attempt laboratory tests of the hypothesis, using erythrocytes for the tests. Oxalated blood was used, this being divided into five parts for control purposes. The crucial tests were made upon two samples, one of whole blood to which small amounts (varying) of glucose were added, and the second to which both glucose and insulin were added. Because of the difficulty of obtaining properly washed corpuscles Secker thought it sufficient to estimate the amount of glucose in the whole blood and compare this with the amount found in the plasma after centrifugation, both containing equal added amounts of glucose and insulin. Results in every case showed that the glucose content of the plasma fell upon the addition of insulin while there was no effect upon the glucose content of the whole blood. This Secker believes must be explained by a change in permeability of the erythrocytes permitting substances in relative excess in either corpuscles or plasma to pass through the cell membranes. Checks by determination of chloride content and also by microscopic observation of the corpuscles in hypotonic and hypertonic salt solutions gave results that could be interpreted in the same way. Guanidine, in the presence of calcium, gave similar results to insulin. Secker suggests that since excision of the parathyroids causes an increase in the guanidines and a decrease in the calcium present that this may be a method by which the parathyroids influence carbohydrate metabolism.—R. J. Seymour.

Influence of nutritive condition on initial fall in blood sugar after insulin. Tiitso (M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23**, 40-43.

Rabbits were starved for one and two weeks and their reaction to insulin tested against that of normal well fed animals. In an hour after injection the blood sugar had been reduced 74.5 mg. per cent in the controls, while it had fallen only 54 mg. in animals starved one week and 48 mg. per cent in those starved two weeks. Starved animals are, therefore, more resistant to the action of insulin than well fed ones.—J. C. D.

Influence of high temperature on insulin (Sulla influenza esercitata dalle alte temperature sulla conservazione dell' insulin). Trocello (E.) & Cruto (A.), Rassegna di clin. terap. (Roma), 1924, **23**, 229-233.

Insulin in a solid state has a greater resistance to heat than insulin in solution. Solid insulin is not destroyed by a temperature of 100° C. for 24 hours, nor of 42° C. for 30 days. The solution has

kept its initial activity at 100° C. for 10 hours, while it is reduced ½ in 24 hours at 100° C., or 16-34 days at 36° C. Such a study is important in relation to the preservation of insulin in tropical regions.—P. M. N.

Heteroplasty of endocrine glands in diseases of the nervous system (Die Heteroplastik der endokrinen Drüsen bei Erkrankungen des Nerven-systems). Brodsky (J.), J. f. Psychol. u. Neurol (Leipz.), 1923-1924, **30**, 77-86; Abst., Physiol. Absts., **10**, 423.

Description of two cases of tetany which were to all appearances completely cured by the intramuscular grafting of the fresh parathyroid glands of a goat. This animal was chosen because the catalase index of its blood (determined by Bach and Zubkowa's method) was the nearest possible to that of the blood of the patients.

The action of Collip's parathyroid extract on blood and cerebrospinal fluid calcium. Cameron (A. T.) & Moorhouse (V. H. K.), Trans. Roy. Soc. Can. (Montreal), 1925, **19**, 39-43; Chem. Abst., **19**, 3524.

Collip's results with parathyroidectomized and normal dogs, and with his standardized extract are confirmed. In the parathyroidectomized animal serum, plasma and cerebrospinal fluid calcium tend to be restored to normal values, and in the normal animal repeated injection raises all three, the ratio remaining constant.

Internal secretions of the parathyroid glands. Collip (J. B.), Proc. Nat. Acad. Sc. (Balt.), 1925, **11**, 484-485; Abst., Chem. Absts., **19**, 3530.

The general principles involved in the preparation of the product are dissolution of the gland by controlled acid hydrolysis and isoelectric fractionation of the active principle. The hormone so obtained is specific for parathyroid tetany in dogs. The physiological effects of the active principle are related mainly to the calcium metabolism. The degree of increase of calcium in the blood is directly related to the amount of the principle which permits a determination of the potency of the extracts.

Further studies on the physiological action of a parathyroid hormone. Collip (J. B.) & Clark (E. P.), J. Biol. Chem. (Balt.), 1925, **64**, 485-507.

Stronger extracts than previously reported (J. Biol. Chem., 1925, **63**, 395) are prepared by the use of methods used for protein purification. The authors find that repeated small doses of this extract produces a cumulative action which ultimately results in

death, while a single large dose causes a transitory hypercalcemia from which the animal always recovers. In the former the intravenous injection of 25% glucose or 15% sodium chloride delays the fatal termination, but there is no complete antidote. The authors offer as a provisional unit the 1/100 of the amount of extract which will produce an average increase of 5 mgms. in the serum calcium of normal dogs weighing 20 kg. over a period of 15 hours. They emphasize the necessity of using a number of animals to eliminate individual differences. Studies of dogs carried to fatal termination show that the N.P.N. increases prior to death, which the authors regard as a terminal phenomenon. Hypercalcemia is produced, which they attribute to the specific hormone action, and total nitrogen and chlorides diminish which they ascribe to the loss of blood. With the establishment of hypercalcemia the blood phosphorous values increase. The degree of hypercalcemia produced by parathyroid injection is greater in normal than in thyroparathyroidectomized animals, but the differences are slight. Blood volume apparently diminishes. The authors were unable to observe any unequivocal influence on blood pressure. Simultaneous administration of potent parathyroid extract and guanidine to normal dogs at regular intervals has resulted in a condition of tetany and of profound hypercalcemia. Death has resulted in such experiments within approximately the same time as in the case of animals receiving parathyroid extract only. The article is illustrated with numerous informative charts.—A. W. R.

Comparable cell changes in central nervous system in cretinism, parathyroid tetany and fatigue. Dye (J. A.), J. Exper. Biol. & Med. (N. Y.), 1925, **23**, 119-121.

The central nervous systems of five cretin lambs and two cretin goats were compared with those of normal animals. Sections were taken from the motor cortex, thalamus, mid brain, cerebellum, medulla oblongata and cervical enlargement of the spinal cord. These were stained by a modification of Nissl's method. Chromatolysis distinct though variable was present in the thyroidless animals. Similar sections from 13 dogs with experimental tetany and from sixteen white rats that had been exercised by swimming showed changes similar in nature though varying in degree.

—J. C. D.

Effects produced by extracts of parathyroid glands on normal and parathyroidectomized dogs. Fisher (N. F.) & Larson (E.), Am. J. Physiol. (Balt.), 1925, **75**, 93-106.

Relatively pure acid extracts of ox-parathyroids were prepared. These extracts were used with decided success for the relief of tetany in a series of eighteen thyro-parathyroidectomized dogs kept

on a meat diet to hasten and increase the severity of tetany. The extracts had a decided action not only in increasing the calcium of the blood serum but the inorganic phosphorus and non-protein nitrogen as well. Some of the animals, after control of the tetany during the first few weeks, did not show any signs of tetany thereafter in spite of a continued low calcium level—below 6 mgm. per 100 cc. of blood serum.—Author's abst.

Parathyroid: An extract obtained from the external bovine parathyroid glands capable of inducing hypercalcemia in normal and thyreoparathyroprivic dogs. Hjort (A. M.), Robison (S. C.) & Tendick (F. H.), J. Biol. Chem. (N. Y.), 1925, **65**, 117-128.

Bovine parathyroid glands were extracted by water, 65% alcohol, acetic acid in alcohol, aqueous and alcoholic sodium hydroxide, ether, acetone, and aqueous and alcoholic hydrochloric acid. An extract which induced hypercalcemia in normal and thyreoparathyroprivic dogs was obtained only when the glands were digested with aqueous or alcoholic hydrochloric acid. It was found that a hormone is obtainable from fresh bovine parathyroid glands by aqueous or alcoholic hydrochloric acid extraction which, when given parenterally to dogs, possesses the property of relieving tetany and inducing hypercalcemia. Boiling the glands with dilute hydrochloric acid is preferable to extraction at room temperature. The lipoid-free portion of the glands is the potentially active tissue. Very little, if any, potency is lost in the removal of proteins by neutralization to the isoelectric point and addition of alcohol to a concentration of 80%. The hormone is relatively stable as judged by the vigorous treatment it withstands in the course of its preparation, and its retention of activity during 16 months preservation in the ice-chest. Definite conclusions are in some cases not justified because of the limited accuracy of the hypercalcemia test.—Authors' Abst.

Histological studies of normal and pathological human parathyroid glands. Kurokawa (K.), Japan Med. World (Tokyo), 1925, **5**, 250-251.

A careful histological study was made of 815 parathyroid glands from 240 human subjects ranging in age from late fetal to 80 years. It was found that anatomically the parathyroids become larger with advance of age, but there is no physiological atrophy. Their development is most marked at the period of adolescence. During the fetal life the parenchyma cells are composed only of clear chief cells. These cells, however, begin to decrease at about the period of adolescence, and the dark cells begin to appear; in adult the dark chief cells predominate. The clear chief cells contain a large quantity of glycogen, but no fatty substance; the dark chief cells contain a large quantity of fatty substance instead of

glycogen. Consequently the quantity of glycogen or fatty substance is influenced by the number of each type of the chief cells. The oxyphile cells begin to appear at about the period of adolescence and there is a tendency to increase. These cells do not usually contain glycogen or fatty substance. If they do it is only in trace. The quantity and the time of appearance of follicles and colloidal formations are about the same as those of the oxyphile cells. The time of appearance and quantitative fluctuation of the dark chief cells and the oxyphile cells begin at the time when the development of parathyroid is most marked, which is the period of adolescence. The oxyphile cells are larger than the chief cells and rich in stainable substances. The protoplasma and nuclei do not show any degenerative changes. The appearance or increase of the oxyphile cells is not accompanied with increase of intercellular tissues, which may be regarded as atrophic changes. The oxyphile cells increase with advance of age, but the increase does not represent senile changes. The oxyphile cells appear in masses and often form nodules, some of which may be seen with the naked eye. The parathyroid gland shows no physiological atrophy. The oxyphile cells appear at the time when the clear chief cells begin to decrease with increase of the dark chief cells and they also increase during pregnancy. These facts indicate that they have some important function.

In status lymphaticus, there was found lipomatosis and atrophy of the parenchyma with marked increase of the oxyphile cells. In adult beri-beri, there is a marked increase of the clear chief cells. In infants the clear chief cells are hypertrophic. In chronic tuberculosis, the increase of intercellular connective tissue is very marked (cirrhosis). In syphilis the picture is about the same as in cirrhosis. In tumor cases, as a rule, the oxyphile cells are increased. In pregnancy, the oxyphile cells are also increased. In sarcoma of bones, there was found marked follicular formations.

—R. G. H.

Observations upon the effects produced in normal and parathyroidectomized dogs and herbivorous animals by injections of parathyroid extract. Macleod (J. J. R.) & Taylor (N. B.), Trans. Roy. Soc. Can. (Montreal), 1925, **19**, 27-38; Abst., Chem. Absts., **19**, 3524.

Collip's results with parathyroidectomized and normal dogs are confirmed. In normal dogs the temperature was raised after the first injection and remained high. Results suggest that fat, either in the diet, or in the fat reserves of the body, may be protective against the action of the extract. Herbivorous animals appear to be resistant to the action of the extract.

Parathyroid extract in treatment of a case of tetany. Snell (A. M.), J. Am. M. Ass. (Chicago), 1925, **85**, 1832-1833; Abst., A. M. A.

A case cited by the author illustrates the effect of Collip's parathyroid extract on the blood calcium level in a clinical case of chronic parathyroid tetany. The marked clinical improvement, the decrease of electrical excitability, and the disappearance of the signs and symptoms of tetany attest the therapeutic value of the substance. The rather large dosage required may possibly be attributed to the relatively low potency of the preparation used. The method of "pyramiding" was used. From 1 to 2 c.c. of the extract was given subcutaneously every two hours, a total of from 5 to 10 c.c. each day. A daily rise in blood calcium was noted, and the average level tended to rise, without, however, reaching normal levels. The diet was maintained at a constant level throughout. All other treatment had been discontinued. Subjective improvement was marked; the patient's restlessness and excitability decreased, and Chvostek's sign was elicited only with difficulty. On the resumption of calcium lactate by mouth, the injection of the extract was discontinued; under this method of management, the serum calcium was relatively constant and the patient appeared to feel fairly well. From 10 to 15 gm. of calcium lactate and 10 c.c. of the parathyroid extract were then given daily. The conjoint use of the two drugs resulted in a rise of the blood calcium to normal, with complete disappearance of every sign and symptom of tetany. Calcium lactate administered alone in maximal dose did not produce and maintain a normal level of blood calcium. The same is true of the dosage indicated for parathyroid extract alone. The combined treatment of calcium and parathyroid easily sufficed to attain and maintain a normal blood calcium level and coincidentally to cause the disappearance of all the signs and symptoms of tetany. The patient feels normal for the first time since the onset of her illness.

The effect of ultra-violet radiation upon experimental tetany. Swingle (W. W.) & Rhinhold (J. G.), Am. J. Physiol. (Balt.), 1925, **75**, 59-69.

Experiments were made on ten dogs using a mercury vapor lamp 30% of the spectral energy of which was in the form of ultra-violet rays. The distance was 40 cm. or less. It was found that exposure of normal dogs to ultra-violet rays for one hour a day for periods ranging from four to twelve days does not appreciably alter the level of the serum calcium. It may even be slightly diminished in some animal. Radiated dogs develop tetany following parathyroid removal as rapidly as normal non-radiated dogs fed the same diet. Radiation of parathyroidectomized dogs greatly prolongs the life of such animals and brings about a striking amelioration of the violent symptoms. Radiated animals may live for twenty-five days

after the first appearance of tetany symptoms, but sooner or later die of tetany or exhaustion. The calcium content of the blood serum of such operated dogs is low and prolonged radiation does not raise it to normal. The amelioration of tetany symptoms by ultra-violet rays and prolongation of life of parathyroidectomized dogs is probably due to the effect of such radiation in increasing the absorption and retention of the small amounts of calcium obtained from the food, so that its elimination from the blood and tissues is less rapid than in non-radiated parathyroidectomized dogs.

—R. G. H.

The effects of parathyroid feeding on calcium and creatine metabolism. Woodman (D.), Bio-Chem. J., (Liverp.), 1925, **19**, 595-600.

Young and adult rats were used for the study. The experimental procedure consisted in the administration either of desiccated parathyroid by mouth or parathyroid extract by injection. The influence of calcium lactate both with and without parathyroid medication was also studied. Muscle creatine, urine creatine and creatinine and bone calcium were all determined by generally accepted standard methods. The author concludes that parathyroid medication has no effect on body weight or on bone calcium. Appetite is increased. No change is observed in muscle creatine which the author explains by the assumption that the muscles are already saturated. The creatine content of the urine increases while the creatinine fraction diminishes under the stimulus of parathyroid feeding. This would seem to indicate that muscle creatine is the precursor of urinary creatinine as Hammett (Am. J. Physiol., 1921, **56**, 196) has shown that the conversion of creatine into creatinine in incubated muscle is inhibited by parathyroid extract.—A. W. R.

The action of parathyroid extracts on guanidine. White (F. D.) & Cameron (A. T.), Trans. Roy. Soc. Can. (Montreal), 1925, **19**, 45-52; Abst., Chem. Abst., **19**, 3524.

Vine's method for estimation of activity of parathyroid preparations shows negligible activity when used with Collip's active extract. The inhibiting influence of complex substances such as arginine or nucliec acid derivatives on the precipitation of guanidine picrate appears to be responsible for the results obtained by Vine's with animal tissues, so that such results probably bear no relation to the functions of these tissues. Marsten's reagent for guanidine estimation reacts with nitro-guanidine and galegine, and slightly with arginine, giving the 2 latter a rose-red color. Parathyroid extracts have little or no effect on guanidine, judged by this test, which excludes change into creatine, creatinine, or methylguanidine. Guanidine picrate is much less soluble in picric acid than in water.

The pineal of birds (La pineale negli ucelli normali e cerebrolesionati). Desogus (V.), Riv. di biol. gen. (Torino), 1924, **6**, 495-504; Abst., Physiol. Absts., **10**, 422.

During sexual activity the glandular cells of the pineal body of birds become larger, and shows signs of secretory activity. The phenomenon is observed in both sexes, but particularly in females. After a cerebral lesion performed during a phase of maximal sexual activity both the germ organs and the pineal body fall into a state of noticeable hypofunction.

Concerning the origin of concretions and pigment in the pineal gland (Uber die Entstehung von Sandkörnern und Pigment in der Zirbeldrüse). Lignac (G. O. E.), Beit. z. path. Anat. u. z. allg. Path. (Jena), 1924-1925, **73**, 366.

The author has made a macro- and micro-scopic study of pineal concretions and discusses their origin from the standpoint of Liesegang's "rhythmic" precipitation of colloids. He likewise discusses the derivation and nature of the pigment bodies. He characterizes the former as spheroliths of concentric structure produced by the simultaneous precipitation of permanent irreversible colloids and of crystalloids. The former function as protective colloids in the gland cell. While nothing is known of their nature, he suggests that they may belong to the myelin group. Two pigmentary bodies are identified. One a yellow substance found in pineal and glia cells and increases in concentration with age. The second is a brownish substance which seems to possess a certain similarity to the skin pigment and is derived from the nuclei of the cells. Those portions staining with pyronin are regarded as a possible source. Several illustrative plates and a brief bibliography accompany the article.—A. W. R.

The influence of the suprarenal gland on the thymus. III. Stimulation of the growth of the thymus gland following double suprarenalectomy in young rats. Jaffe (H. L.), J. Exper. M. (Balt.), 1924, **40**, 753.

In view of the fact that previous observations showed that double suprarenalectomy in the rat, if carried out after involution had normally begun, brought about regeneration of the thymus gland, it was decided to study the effect of suprarenalectomy on young rats before puberty or before involution of the thymus had set in. The material included a study of 39 young rats, varying in age at operation between 35 and 54 days. Twenty-five of these rats were suprarenalectomized. Of these 25, 11 died from 1 to 41 days after the extirpation and were excluded from the experiments proper. The remaining 14 were sacrificed at two weeks' intervals from 2 to 8 weeks after operation and the weights of their thy-

muses compared with those of 14 control rats. Eleven of the control rats were litter mates of the animals operated upon. The thymus gland of each of the 14 suprarenalectomized rats was heavier than that of its respective control, the difference varying from 12% to 85%. The average thymic weight of the 14 suprarenalectomized rats was 49% greater than that of the controls. This thymic hyperplasis was apparent soon after suprarenalectomy, the maximum effect being attained usually within two weeks. Prepubertal thymic hyperplasia following suprarenalectomy may offer a partial explanation of the pathogenesis of status lymphaticus. In the human cases, hypoplasia of the suprarenals is one of the outstanding pathological findings together with a large thymus and prominent lymph nodes. While earlier authors emphasize the hypoplastic changes of the chromaffin tissue, the later work of Marine and Baumann on the rabbit and our work on the rat clearly indicate that the lymphoid overgrowth is dependent upon interrenal and gonadal insufficiency.—Author's Abst.

Experimental studies on the formation of Hassall's corpuscles. Jaffe (H. L.) & Plavska (Alexandra), J. Exper. Biol. & Med. (N. Y.), 1925, **23**, 91-93.

Autoplastic transplants of the thymus were made in guinea pigs 30 to 45 days old. The microscopic changes in the transplants were followed for 48 days. The authors conclude that these studies seem to bring unequivocal experimental proof that Hassall's corpuscles are derivatives of the reticular epithelium, a view originally proposed by Paulitsky and more recently elaborated by Hammar, and supported by many others on the basis of embryological and post fetal histological studies. They also show that in post fetal life the formation of Hassall's corpuscles is independent of the presence of remnants of the original epithelial ducts of Remak.—J. C. D.

Influences of the constituents of thymus gland cells on the growth of young organism. Miyagawa (Y.) & Wada (K.), Japan Med. World (Tokyo), 1925, **5**, 275-289.

Aqueous extract of calves' thymus gland was injected into a considerable number of young white rats and a few young dogs. The work was controlled by similar injections of kidney or lymph node extracts. With optimal doses of thymus extract (0.05 gm. thymus per kg. body weight) a marked accentuation of growth was observed, with larger doses (1.0-2.0 gm.) growth was retarded, presumably on account of toxic effects. In a few instances extracts of thyroid gland were found to depress growth.—R. G. H.

Skeletal changes in human fetuses as a result of undernourishment of the mother during pregnancy (Die Änderungen im Knochen-

system der Früchte während der Schwangerschaft bei Unterernährung). Stefko (W.), Ztschr. f. Konstit. (Berl.), 1925, **10,** 742-754.

In examining human fetuses from 4 to 7 months and newborn in which the mother had been undernourished to various degrees, the obvious endocrine change in the offspring was an unusually early involution of the thymus.—A. T. R.

Observations on effects of iodine administration in dogs following hemithyroidectomy and unipolar ligation. Barber (W. H.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23,** 167-169.

There was much less hyperplasia of the thyroid cells in this series than in a previous series of dogs similarly operated upon in which iodine was not given.—J. C. D.

Adenomatosis, or the diffuse adenomatous goiter. Else (J. E.), J. Am. M. Ass. (Chicago), 1925, **85,** 1878-1882; Abst., A. M. A.

Else asserts that adenomatosis of the thyroid is a definite pathologic entity differing from adenoma in that the process is diffuse and does not have a true capsule. Adenomatosis produces a hyperthyroidism of the cardio-vascular type. It is important to differentiate between adenoma and adenomatosis because the former requires simple enucleation of the tumor growth, while the latter requires subtotal double lobectomy.

Autolysis of the thyroid gland. Ferrero (V.), Arch. d. sc. med. (Par.), 1925, **47,** 294-301; Abst., Chem. Absts., **20,** 58.

In small pieces of the canine thyroid subjected to aseptic autolysis there occurs from the fourth to the sixteenth hour a gradual destruction and final complete dissolution of the alveolar colloid, preceding the alterations occurring in the thyroid tissue itself. This is believed to indicate the presence in the gland of an enzyme capable of rendering the colloid soluble and hence capable of absorption during life.

Osseous and muscular changes in thyroidectomized sheep. Goldberg (S. A.) & Simpson (S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23,** 132-133.

In cretin sheep and goats the abdomen and digestive tract were flabby and distended. The femurs were atypical with an increase in red marrow, a persistence of epiphyseal cartilages and other changes. The skeletal and cardiac muscle showed changes, particularly a practically complete absence of cross striations. These changes seem to indicate that as a result of the thyroidectomy there are degenerative changes following an arrested development of the osseous and muscular tissues.—J. C. D.

Hypothyroidism. Grigsby (C. M.), South. M. J. (Birmingham), 1926, **19**, 4-5.

The author discusses larval myxedema, as contrasted with cretinism and marked progressive myxedema. He gives the symptoms emphasizing the reduced metabolic rate as an important one and then outlines the treatment. He uses thyroid extract starting with small doses and gives thyroxin only in obstinate cases.

—J. C. D.

The changes in the blood sugar which follow experimental thyroid feeding. Hancher (K. G.), Hupper (Marjorie), Blau (N. F.) & Rogers (J.), Am. J. Physiol. (Balt.), 1925, **75**, 1-5

The oral administration to 32 dogs of a glycerol extract of hashed fresh (pig) thyroid glands produced a marked and sustained rise in the sugar content of the animal's blood. This was not shown by any of four commonly used commercial preparations of the medicament. One of these, in fact, caused an immediate and distinct decrease in the blood sugar.—R. G. H.

Iodin hyperthyroidism—an analysis of 50 cases. Jackson (A. S.), Boston M. & S. J., 1925, **193**, 1138.

The appreciation of the value of iodine in the treatment of goitre has resulted in its indiscriminate and unwise use both by physicians and the public, so that the incidence of iodine hyperthyroidism is increasing. In 40 of the 50 cases iodine had been prescribed by a medical man. In iodine hyperthyroidism the pulse does not have the low diastolic pressure found in exophthalmic goitre. The basal metabolic rate in this series averaged 31% plus, in a group of toxic adenoma, 29%, and in a series of exophthalmic goitre cases, 54% plus. The disorder of the gland resembles toxic goitre. Three patients in this series died. Eleven were treated medically and the rest by operation. Of the forty for which there are proper records all showed a marked reduction in metabolic rate and a gain in weight.—J. C. D.

Induced hyperthyroidism. Kimball (O. P.), J. Am. M. Ass. (Chicago), 1925, **85**, 1709-1710; Abst., A. M. A.

In order to determine if possible whether or not harm may result from the routine use of iodin in the prophylaxis of goiter as it has been carried out in the Cleveland district since 1917, a study has been made by Kimball of those cases of hyperthyroidism in which some form of iodin has been administered. In 309 cases it appeared that the symptoms of hyperthyroidism had been precipitated or made worse by the use of iodin. In 210 cases the goiters were of long standing, the average period being eighteen years. In each of these cases, the gland was clinically or microscopically

adenomatous. In this group of 309 cases, there were six cases in which the only source of iodin had been iodized salt. All of these patients were women past 40 years of age, and each had a nodular goiter of long standing. Thirty-seven patients had taken iodin of their own volition; several had taken a solution of sodium iodid, but the great majority had used repeated external applications of tincture of iodin over the goiter. The most striking fact brought out by this study is that five-sixths of the patients having induced hyperthyroidism had been taking iodin as prescribed by their physicians. In twenty-one cases of goiters of long standing, compound solution of iodin (Lugol's solution) had been given for weeks, in doses of from 5 to 10 drops, three times a day. In many cases, 5 drops of the solution of sodium iodid, three times a day, had been prescribed, and a considerable number of these patients had taken this medication for as long as three or four months. One boy, aged 16 years, who had a congenital adenoma, had taken syrup of ferrous iodid, 1 dram (3.75 c.c.), three times daily, continuously for eighteen months. In 84 per cent of the cases of toxic goiter the physicians had prescribed large doses of iodin to be taken over a long period of time, and this treatment had been given in spite of the fact that the goiter was of long standing and in many cases, nodular in type. Kimball says that, in all cases of iodin treatment, the dosage should be considered in terms of milligrams. The maximum dosage for an adult, provided there are no contraindications, is 10 mg. daily for not longer than one month, during which time the patient should be under very close observation. Long standing goiters in adults should be treated surgically, if any symptoms of hyperthyroidism are present. In young adults and in adolescents, medical treatment should first be tried. There is apparently no danger in the routine prophylaxis of goiter as it is carried out through the schools; namely, the administration of 10 mg. of iodin weekly. Among forty cases of exophthalmic goiter in children, only one child had been given iodin. In this case the patient had received the prophylactic treatment of 10 mg. of iodin a week for one month, three months before the onset of the acute hyperthyroidism, and a review of the history shows that the onset of the hyperthyroidism in this case was a coincidence and not a result of the month of iodin treatment. In the medical treatment of goiter in adults, Kimball emphasizes the importance of care in the selection of cases; the use of small amounts of iodin for not longer than one month, and the necessity of close observation throughout this period.

Studies in endocrinology. Hypothyroidism with and without myxedema. Lawrence (C. H.), Boston M. & S. J., 1924, **190**, 8-21.

This article is based on a clinical and laboratory study of twenty-five cases of hypothyroidism, all adults. There were twenty-

one females and four males, the usual ratio in thyroid failure. In only four cases was there a family history of endocrine disease. In fourteen cases the onset of the failure was referred by the patients to an acute infection or strain. In the remainder there was no definite etiology obtained in the history. The average duration of the condition was over eight years, showing how frequently hypothyroidism escapes detection. The author reports fully on a case of thyroid failure without myxedema, giving the physical and laboratory findings, before and after treatment, and emphasizes the existence of a non-myxedematous type of hypothyroidism which is often not recognized by the clinician. Eight of the patients in his series were of this type. The various findings in all the cases are tabulated. Attention is called to the high blood nitrogen in the majority of cases and the question is raised concerning the possible relation of abnormal nitrogen metabolism to the early arteriosclerosis of hypothyroidism. The author emphasizes the more simple tests which should at least raise the suspicion of thyroid failure in the absence of myxedema.—Author's Abst.

Exophthalmic goiter question. Liek (E.), Deutsch. Ztschr. f. Chir. (Leipz.), 1925, **193**, 246; Abst., J. Am. M. Ass., **85**, 1845.

The author emphasizes the significance of the brain in the pathogenesis of exophthalmic goiter. He has scarcely ever encountered a case without a history of some grave psychic trauma. Psychoanalysis may help in treatment, in the beginning as well as before and after surgical treatment. He prefers the latter to roentgen therapy except in adolescents. The operation should be made in a favorable phase of the disease. The mental condition of the patient is prognostically more important than the basal metabolism. The intervention should be extensive, but without attempt to get the thymus. He deplores the frequent overlooking of the psychic condition by self-styled "sober thinking" surgeons and attributes it to the loss of mental versatility occurring in every mechanism of mental work. This leads to a sort of self-righteous mandarin attitude, and wrong judgment as to success and failure.

Blood flow and blood pressure in exophthalmic goiter. Liljestrand (G.) & Stenström (N.), Acta Med. Scand. (Stockholm), 1925, **43**, 99-129.

The minute volume of the heart during rest was determined in 7 females and 3 male healthy subjects and in 8 females and 3 males suffering from exophthalmic goiter. A considerable increase in the minute volume was found in the diseased subjects, amounting on an average in the female patients to 80%, in the male to 100%. The utilization of the oxygen of the blood was somewhat lower than normal, so that in addition to the increased metabolism

other factors may also have been responsible for the augmented blood flow. The systolic blood pressure in the patients was somewhat increased, the diastolic pressure showed a slight decrease. The considerable increase in the work of the heart which is a consequence of the increase in minute volume and mean blood pressure, seems to play an important part in the development of those symptoms from overstrain of the heart which often occur in exophthalmic goiter.—Author's Summary.

Development of the pineal gland in infancy (Die Entwicklung der Zirbeldrüse in Säuglingsalter). v. Meduna (L.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1925, **76**, 534-547.

Meduna concludes that on the whole the development of the pineal gland indicates that it is an endocrine organ. The parenchymal cells, while regarded as sui generis, are related to the glia cells, having a common ectodermal origin.—A. T. R.

The interaction of thyroid and adrenals as shown by the respiratory metabolism (Das Zusammenwirken von Schilddrüse und Nebenniere, geprüft am respiratorischen Stoffwechsel). Nakayama (K.), Biochem. Ztschr. (Berl.), 1925, **155**, 386-412.

The author has studied the respiratory metabolism of rats by the differential method with controls (Asher-Takahashi, Biochem. Ztschr., 1924, **145**, 130). The adrenal influence is studied by suprarenin injections, using both the subcutaneous and intramuscular routes. Normal rats under these circumstances exhibit great increases in the oxygen consumption and carbon dioxide elimination. Thyroidectomy inhibits this action very markedly, although the injections produce the same qualitative result. The simultaneous use in normal rats of suprarenin injections and thyroid extract by mouth produces very great increases in the metabolic level which is repeated although in lesser degree when previously thyroidectomized rats are used. By a careful study of the time element the author feels that he has demonstrated that a slower rate of absorption is not the inhibiting factor in the experimental animals. He concludes that the thyroid hormone is a potent activator of the parasympathetic and sympathetic nervous systems. This conclusion is not modified by the fact that the activation of adrenalin by the thyroid is not rigorously specific. The article contains very complete protocols of the experimental results.

—A. W. R.

The effect of extirpation of thyroid and spleen on the basic respiratory metabolism as influenced by injections of suprarenin (Über

die Wirkung von Schilddrüsen und Milzexstirpation auf den durch Adrenalininjektion beeinflussten respiratorischen Grundumsatz). Nakayama (K.), Biochem. Ztschr. (Berl.), 1925, **155**, 436-458.

The third paper in the series (Biochem. Ztschr., 1925, **155**, 387 and 413) using similar methods. The author finds that the removal of the spleen after thyroidectomy still further lessens the stimulating action of suprarenin injections initially produced by thyroidectomy alone. The complete removal of the spleen from otherwise normal animals may inhibit the response of the organism to suprarenin, but does not necessarily produce this result. The simultaneous removal of both thyroid and spleen produces divergent and contradictory results, in some instances increasing, in others decreasing the effect on the gaseous metabolism of suprarenin injections. If the spleen be first removed and later there be extirpation of the thyroid, the subsequent use of suprarenin, subcutaneously administered, may cause a notable increase in the gaseous metabolism. Full protocols are included.—A. W. R.

Present-day surgical treatment of diseases of the thyroid gland. Pemberton (J. D.), J. Am. M. Ass. (Chicago), 1925, **85**, 1882-1886; Abst., A. M. A.

In the Mayo Clinic, in 1924, there were 1,928 operations on 1,725 patients with goiter. Ten patients died, a mortality by operation of 0.51 per cent and by case of 0.58 per cent. There were 677 patients with goiter unassociated with hyperthyroidism, with no deaths; 368 patients with hyperfunctioning adenomatous goiter, with four deaths (1.08 per cent), and 741 patients with exophthalmic goiter, with six deaths (0.8 per cent). This extremely low mortality rate achieved by present-day surgical treatment of the thyroid gland, according to the author, was made possible by the perfection of operative technic and the discovery of means of controlling hyperthyroid crises. The employment of the multiple-stage operation in selected cases, and refinements in management designed for the protection of the patient resulted in a tremendous reduction in the operative mortality and served to establish firmly the surgical treatment of exophthalmic goiter. However, on account of the failure to eliminate the hyperthyroid crises completely, and because of the obvious objections to the multiple stage operation, this method left much to be desired. The proper administration of iodin to patients with exophthalmic goiter has completely controlled both the spontaneous and the postoperative hyperthyroid crises. The influence of iodin on the surgical treatment of exophthalmic goiter

is shown by the following clearly proved facts: 1. The convalescent period has been definitely shortened. 2. The necessity for multiple operations has been greatly decreased. 3. The limits of operability have been widened. 4. The mortality has been further reduced. The problem presented by the patient with hyperfunctioning adenomatous goiter is one of procrastination, and the hope of its solution lies in the education of the public to the fact that all nodular goiters are potentially dangerous and should be removed unless the patient is kept under periodic medical observation.

Iodids in substernal goiter in childhood. Petemyi (G.), Monastschr. f. Kinderh. (Leipz.), 1925, **30**, 419; Abst., Am. J. Dis. Child., **30**, 881.

In two cases in which substernal goiters produced such pressure symptoms as to suggest the necessity of operation, potassium iodid in doses of 25 mg. twice a day relieved all the symptoms.

The histological changes brought about in cases of exophthalmic goiter by the administration of iodine. Reinhoff (W. F., Jr.), Johns Hopkins Hosp. Bull. (Balt.), 1925, **37**, 285-306.

Brief historical sketch pointing out the close relationship of iodine to endemic goiter as well as the physiological hypertrophies in man and animals. Three clinically typical cases of exophthalmic goiter are reported. In each of these the basal metabolic rate was well above fifty. (Since this report five more cases have been so studied with similar results.) Iodine had not been administered in any form. Under local anaesthesia one entire right upper pole of thyroid gland was removed. It was fixed in Zenker-formalin and embedded in paraffin. Serial sections revealed the characteristic microscopical picture of exophthalmic goiter. The patients then received Lugol's solution, 10 minims, 4 times daily for 2-3 weeks. In all cases the patients improved markedly, the pulse and basal metabolic rate becoming normal. Double partial lobectomy was then performed and the gland compared in gross and microscopic features with the portion removed at first operation. The following changes had occurred. The gland increased in size, became more hard or rubber like in consistency and nodular in contour. Thrill and bruit at the poles had disappeared. Vascularity decreased with marked increase in amount and density of colloid. Scarring as well as the fibrous stroma of the gland was augmented. Involutional sequelae in the form of large colloid cysts, localized and encapsulated, dilated colloid acini resembling so-called colloid

adenomata were seen. The bulging, active epithelial cells which before iodine was given contained large vesicular nucleus and colloid-like droplets after iodine were shrunken, containing no colloid droplets and pycknotic nuclei. The blood vessels were collapsed and some thrombosed. The acini which were papillomatous and lace-like before iodine were more regular in contour and distended to maximum capacity with colloid. Fifteen other cases studied gave similar findings. The series shows that iodine produces an artificial clinical remission in cases of exophthalmic goiter, which is accompanied by a change in the histological picture from hyperplastic to a colloid state. The colloid state, therefore, clinically, as well as histologically, is less active than the hyperplastic state. A clinical remission, artificial or natural, in a case of exophthalmic goiter, is associated with a change in the histological picture from a hyperplastic to a colloid state. There may be enough hypertrophy and hyperplasia remaining after the clinical remission to characterize the tissue histologically as exophthalmic goiter, but when compared to the same gland before the remission, it is evident that relatively the histological hypertrophy and hyperplasia is markedly less. The degree of hypertrophy and hyperplasia present depends on the clinical course of the disease, in regard to the remission and exacerbations, either natural or artificial. Involutional sequelae resembling, histologically, certain benign tumors of the thyroid gland occur following artificial remission, i. e., so-called colloid adenomata and colloid cysts.—Author's Abst.

Quantity and relation between cholesterine and total fat acids of the blood serum in experimental hyperthyroidism (Sulla quantitaed il rapporto fra colesterina e acidi grassi totali del siero di sangue nell' ipertiroidismo sperimentale). Sestini (C.), Biochim. e terap. sper. (Milano), 1925, **12**, 293-306.

Small quantities of thyroid extract fed for a few days to the rabbit lessens the quantity of fatty acids in the blood serum and increases the cholesterol to a variable extent. Increasing the dosage and the period of feeding causes a decrease in both of these substances. Only large doses over a long period of time can cause hypercholesterolemia. Fatty acids and cholesterol react oppositely in this respect.—P. M. N.

The treatment and prognosis in myxedema. Sturgis (C. C.) & Whiting (W. B.), J. Am. M. Ass. (Chicago), 1925, **85**, 2013-2017; Abst., A. M. A.

Sturgis and Whiting report their observations on a series of

twenty-six patients, all of whom presented the typical symptoms and signs of myxedema and, in addition, all had a characteristically diminished basal metabolism. Dried thyroid gland (Armour's) was used in all cases. Treatment was controlled by (1) the clinical response of the patient, (2) the basal metabolism, (3) the resting pulse rate, and (4) the body weight. The amount of dried thyroid gland which is necessary to restore the basal metabolism from the initial low point to normal has varied widely, as the total amounts necessary in this series have ranged from 2.3 to 6.5 gm. This variation has been due, in part at least, to the lack of a constant time interval over which the drug has been given. Experience has suggested that sex, age, body weight, duration of the disease, severity of the symptoms, and the initial level of the metabolism bear no accurate or constant relationship to the amount of thyroid gland necessary to restore the patient to a normal condition. In the average adult patient without complications, it has been found that a dosage of 0.13 gm. (2 grains) three times a day can be continued with safety until the basal metabolism and pulse reach normal. With this dosage, the metabolic level and pulse rate usually reach normal in from five to ten days, although individual patients show a wide variation in this respect, and it is advisable, therefore, to keep the patient under close observation and continue with this amount until satisfactory results are obtained. In treating patients with uncomplicated myxedema, it is more satisfactory to confine them in a hospital for from two to three weeks, as this permits close observation and their activity can be controlled. As profound changes occur in the patient's metabolism during the early stages of treatment, it is desirable to keep them in bed for at least a week as a precaution against unpleasant symptoms. If the patient is under observation in a hospital, the initial dosage of 0.13 gm. (2 grains) three times a day is continued until the metabolism and resting pulse rate approach normal and there is clinical evidence of improvement. After thyroid gland has been given in amounts of 0.13 gm. three times a day for three or four days, the first clinical evidence of a thyroid effect is shown by the patients experiencing a sensation of increased warmth, moderate sweating and accelerated mental reactions. Coincident with these changes, there is usually a slight increase in the resting pulse rate, averaging about 10 beats a minute, and, likewise, the basal metabolism shows an average rise of 10 per cent. At this time, the patient's temperature may become somewhat elevated above normal for a few days, the average, however, not exceeding 100 F. The drug should be continued until the basal metabolism is between —10 and —5,

according to the standards of Du Bois. While it is generally accepted that the normal varies between —10 and +10 according to these standards, it has been the author's experience that the average patient with myxedema more nearly approaches a condition approximating normal if the metabolism is maintained between —5 and —10. If the metabolism remains at this level for five or six weeks, there will be a loss of weight which averages from 10 to 15 pounds (4.5 to 6.8 kg.). This loss is due apparently to the disappearance of the subcutaneous, nonpitting edema that is characteristic of the disease. After several months of treatment, it is commonly observed that the patients regain this weight and 5 or 10 pounds (2.3 or 4.5 kg.) in addition, which doubtless results from their greatly improved general nutrition. After the patient's basal metabolism and pulse rate have been restored to normal and there has been evidence of clinical improvement, the second stage of treatment is begun. The object of this time is to determine the exact dosage which will maintain the metabolism at the proper level. This has been called the maintenance dose, and is the amount that is to be taken by the patient each day. This dosage when once established is usually constant and in most instances must be continued throughout a patient's life, although occasionally the size of the dose must be altered, and in very rare instances it appears that there may be complete recovery from myxedema, as the drug may be discontinued without a recurrence of the disease. Most frequently the correct dose is in the vicinity of 0.13 gm. (2 grains) a day, although in individual patients the amount has varied from 0.065 gm. (1 grain) to 0.195 gm. (3 grains) daily. In a study of twenty-five patients with myxedema who have been observed over a sufficient length of time to make results significant, fourteen required a maintenance dose of 0.13 gm. (2 grains) daily; six, a dose of 0.195 gm. (3 grains); two a dose of 0.065 gm. (1 grain), and three, a dose of 0.098 gm. (1.5 grains). Occasionally a patient has taken as much as 0.39 gm. (6 grains) as a maintenance dose for a short period, but this amount has invariably produced symptoms of overdosage if continued for any length of time. There are several complications that may exist in patients with myxedema which make the administration of thyroid gland a somewhat hazardous procedure unless the treatment is very carefully controlled. The complications involve chiefly the heart, kidneys and blood and are observed more frequently in the middle-aged or elderly patients. Illustrative cases are cited.

Experimental study on the etiology of goiter (Experimenteller Beitrag zur Aetiologie des Kropfes). Tanabe (H.), Beit. z. path. Anat. u. z. allg. Path. (Jena), 1924-1925, **73**, 415.

The authors present the details of the influences of calcium excess and iodine lack on the production of goiter. Selecting rats as the experimental animals a long series of feeding experiments were instituted. Meat, barley and endive constituted the basic ration and to this was added or omitted potassium iodide and calcium salts in varying amounts. The thyroid dimensions and histologic findings are fully tabulated and discussed. The author concludes that his basic diet alone will produce goiter while an unregulated mixed feeding will not; that distilled and tap water are both without influence. He concludes that lack of iodine is the basic etiologic factor and that calcium in appreciable amounts promotes goiter growth only where there is simultaneous poverty of iodine. Very small amounts of potassium iodide are sufficient to inhibit glandular hyperplasia.—A. W. R.

Hypothyroidism. Taylor (W. A.), Northwest Med. (Seattle), 1925, **24**, 422; Abst., Am. J. Dis. Child., **31**, 124.

The author considers the following conditions due to hypothyroidism. In obesity, dietary restriction usually suffices, but thyroid will hasten the result and is safe if the basal metabolism is watched. In thin, weak, and listless patients with anorexia, minute doses of thyroid are of benefit. Thyroid is of value in young girls with severe dysmenorrhea. Women at the menopausal age with swelling of the hands and feet are helped by thyroid. Colloid goiter and goiter of puberty are usually benefited by thyroid extract, as are long standing cases of exophthalmic goiter which have become hypothyroid. He considers infantile myxedema in the congenital form, in the early form appearing during the first year, and in the mild, attenuated form which is difficult to recognize and is characterized by failure of mental and physical development. The author's dose of dry thyroid extract averages 0.01 gm. for every 6 months of age, minimum dose 0.001 gm., maximum dose 0.05 gm. He recommends alternation of treatment and rest periods.

Effect of domestication and culture on cranial form and body build (Domestikation und Kultur in ihrer Wirkung auf Schädelform und Körpergestalt). Weidenreich (F.), Ztschr. f. Konstit. (Berl.)) 1925, **11**, 1-52.

The thyroid gland is mentioned as being especially connected with certain bodily features as is evident in cretinism.—A. T. R.